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Composition of Pablum

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Oatmeal	18
Wheat Germ	15
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Powdered Beef Bone	2
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Sodium chloride	1
Alfalfa Leaf	1
Dried Brewers Yeast	1
Reduced iron	
(11 Gm. per 100 lbs.)	

Approximate Analysis of Pablum

Carbohydrate (by difference)	69.9%
Protein (N X 6.25)	15.0
Moisture	7.0
Minerals (ash)*	4.2
Fat (ether extract)	3.0
Crude Fiber	0.9
*Including:	
Calcium	0.78%
Phosphorus	0.62
Iron	0.03
Copper	0.0013

Approximately 106 Calories per oz. or 3.7 per Gm. 12 level tablespoonfuls = 1 oz.

Each ounce contains not less than 0.3 mg. thiamine (vitamin B₁) and 0.1 mg. riboflavin (vitamin G).

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VOLUME 6, NUMBER 5

MAY, 1946

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

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VOLUME 6, NUMBER 5

GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

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ANNOUNCEMENTS

Meetings

American Gastro-Enterological Meeting—Friday and Saturday, May 24th and 25th.

American Gastrosopic Club—Sunday, May 26th.

American Society Clinical Investigation—May 26th, 27th, 28th.

American Association of Physicians—May 26th, 27th, 28th and half-day the 29th.

Meeting of the Association

The American Gastroenterological Association will meet at Atlantic City, May 24 and 25, 1946. The meetings will be held at the Hotel Claridge.

The Scientific Sessions will start Friday, May 24th, at 1:30 P.M. The Sessions will be concluded Saturday afternoon at 5:00 P.M. The Banquet of the Association will be held Saturday evening. The Society for Clinical Investigation and the American Association of Physicians are scheduled to meet the following week in Atlantic City. Hotel reservations should be made early.

American Board of Internal Medicine

The next written examination of this Board will be held on October 21, 1946. The closing date for acceptance of applications for this examination will be July 1, 1946. For particulars address Dr. William A. Werrell, One West Main Street, Madison, Wisconsin.

Information Regarding Post-Graduate Instruction in Gastroenterology

At the request of the Board of Governors of the American Gastroenterological Association, Dr. Julian M. Ruffin wrote the members of the Association to ascertain those members and institutions which were able to provide a short course or extended graduate study in Gastroenterology. The following have responded.

Those who are interested in obtaining such instruction should write promptly to the person or school of their choice, because in most instances the number of students who can be accommodated is limited.

<i>Name</i>	<i>Place</i>	<i>Name</i>	<i>Place</i>
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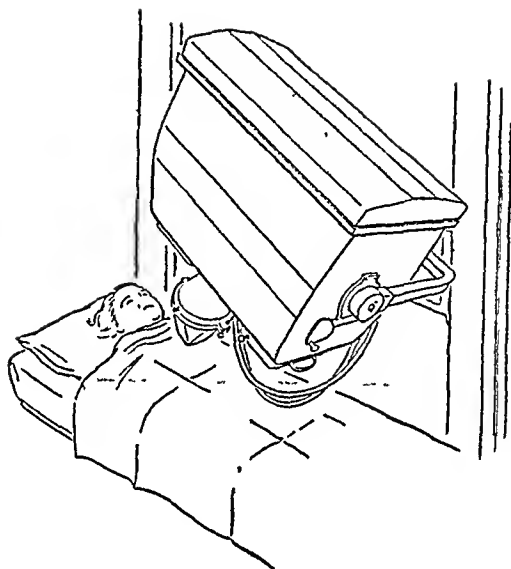


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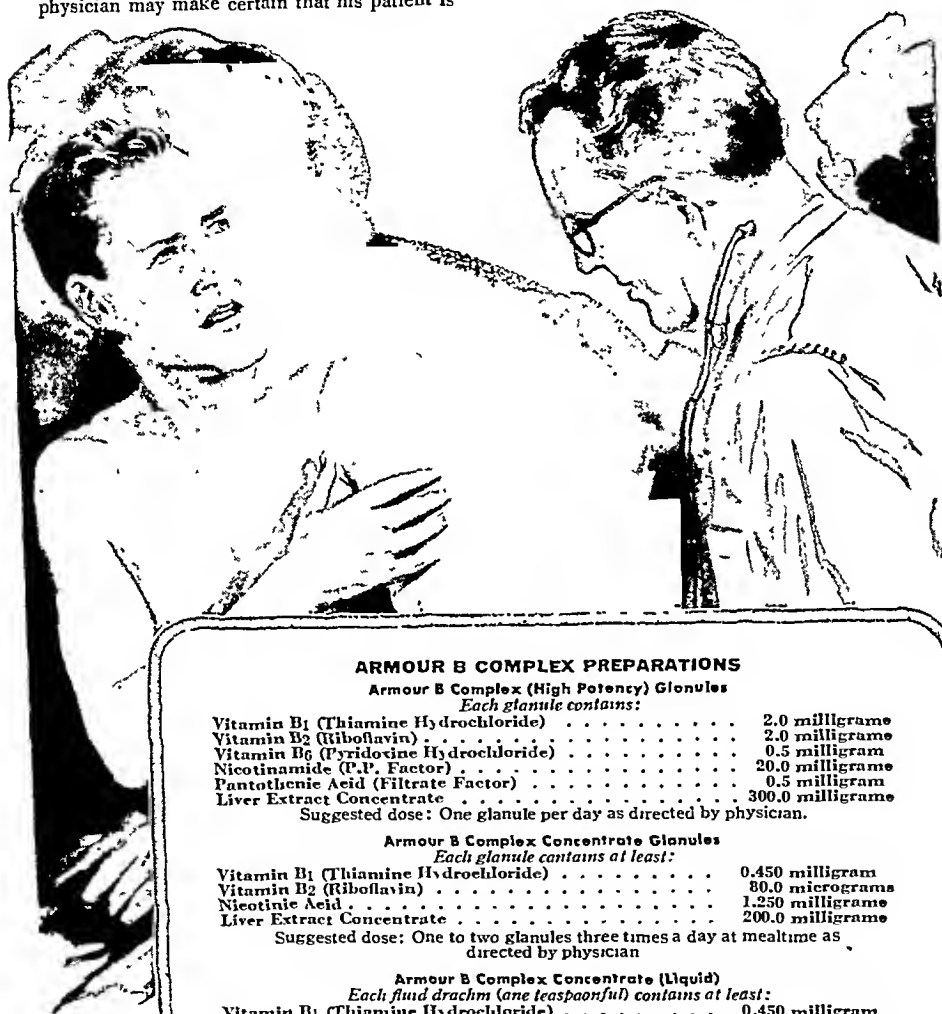
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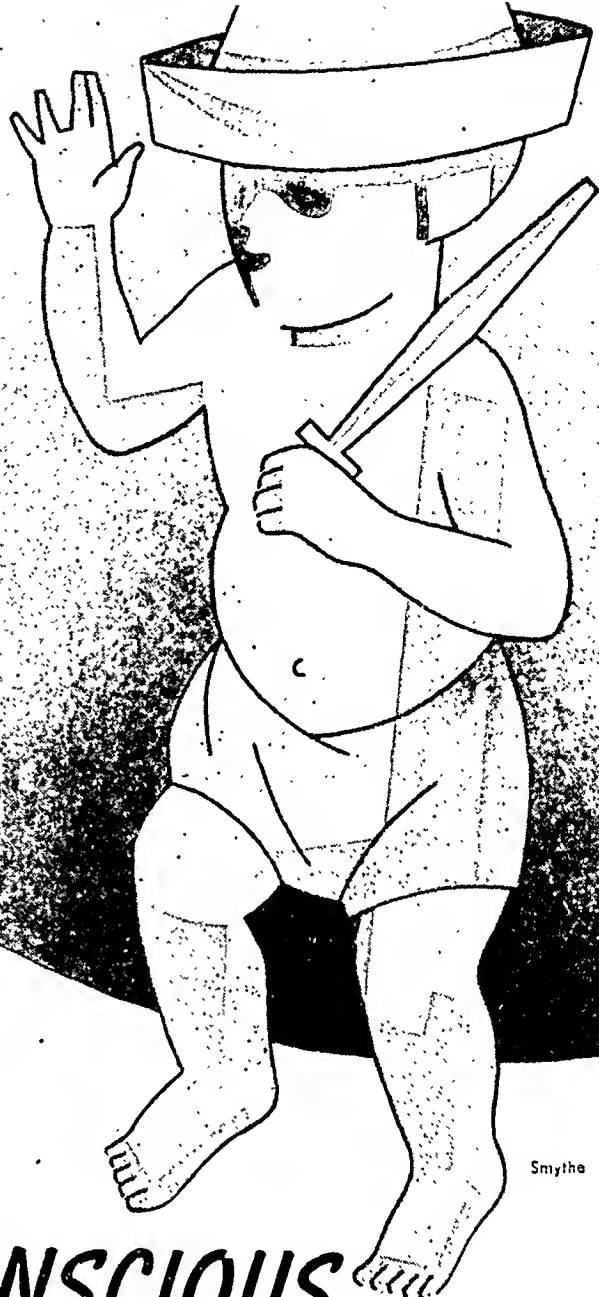
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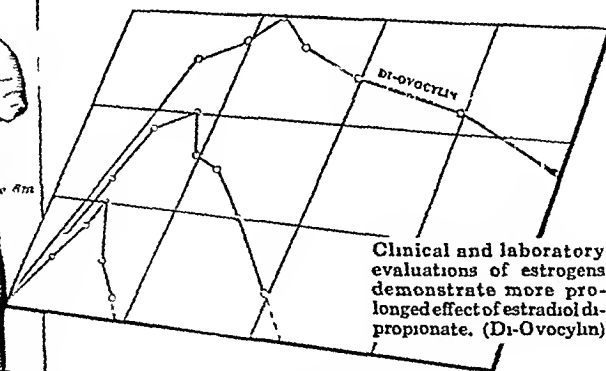
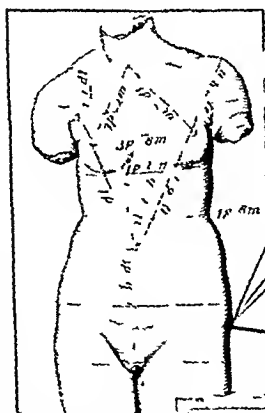
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*Greene, R R, Int Abst Surg 74 595, 1942

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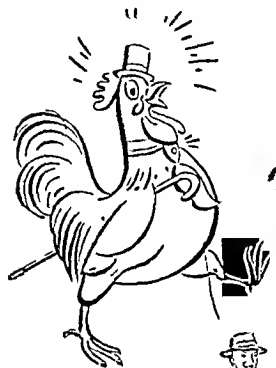
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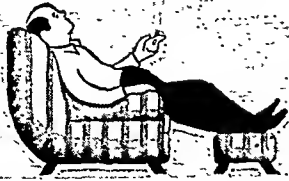
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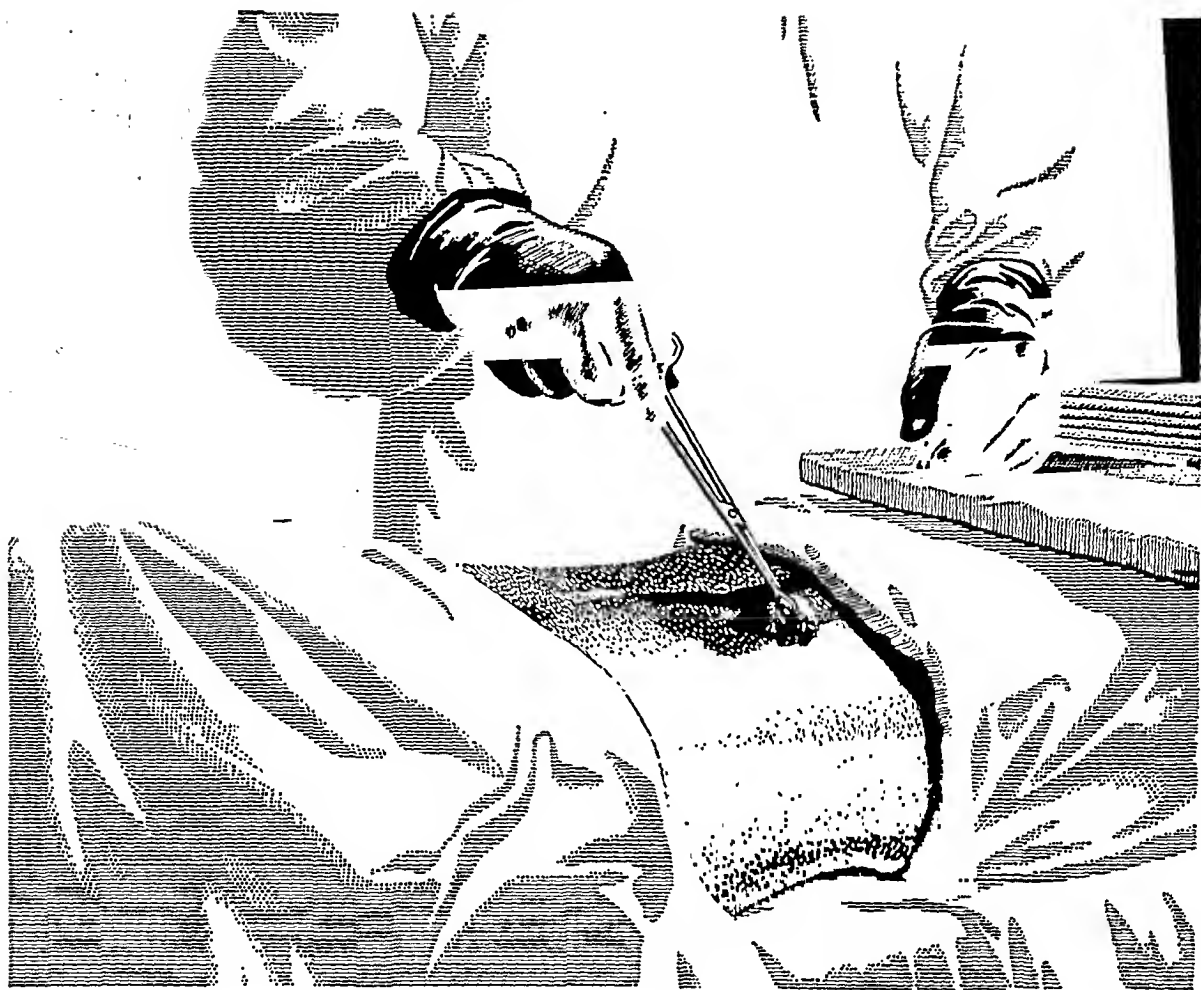
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GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

VOLUME 6

MAY 1946

NUMBER 5

HEPATITIS AS OBSERVED IN AN ARMY GENERAL HOSPITAL¹

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INTRODUCTION

This study consists of an analysis of 200 patients with hepatitis observed in the wards of the William Beaumont General Hospital. Included are 110 cases of acute infectious hepatitis, 33 cases of acute hepatitis following plasma transfusion, and 57 cases of chronic hepatitis resulting from acute infectious or post vaccinal hepatitis. The term chronic hepatitis is used arbitrarily to designate the recurrence or persistence of symptoms for a period longer than six months. More than half of the patients were previously hospitalized elsewhere and their records were available for study and comparison. Observation of patients in this series was continuous from the time of admission until the completion of treatment and disposition.

In the study of these patients, routine roentgen examinations and other laboratory studies were done to exclude diseases other than hepatitis. Patients with evidence of peptic ulcer, cholecystitis, parasitic infestation, or other disease of the gastrointestinal tract were excluded. Cases of jaundice due to causes other than hepatitis were eliminated. In the determination of liver enlargement, the physical examination included examination of the upper and lower borders of that organ; when indicated, an x-ray film was employed. For routine liver function studies, bromsulphthalein, cephalin flocculation, and serum albumin and globulin were employed. The icterus index was most convenient for estimating jaundice. Serial tests were done at regular intervals with above mentioned methods. Other liver function studies were done only occasionally.

ACUTE HEPATITIS

Onset. The symptoms preceding the appearance of clinical jaundice have been referred to as prodromal (1). This designation creates the assumption that hepatitis is synonymous with jaundice. Actually the hepatitis begins with the first symptoms. While jaundice is the most prominent symptom of the disease, it is not necessarily an index of the date of onset. Indeed, jaundice that is sometimes considered as a case of acute hepatitis during an epidemic

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may be merely the first manifestation of icterus in a patient in whom the disease is already chronic. While it is true that in many patients the pre-icteric symptoms abate in varying degree after the appearance of jaundice, it is not the rule. The symptoms may persist through the period of jaundice and long after the jaundice has subsided.

The character of onset was recorded in 153 cases of infectious hepatitis. In 50 per cent the pre-icteric symptoms were gastro-intestinal in character. In about one half of these the introductory symptoms were nausea and vomiting; in the other half the symptoms were more insidious, consisting of anorexia, nausea, abdominal pain and diarrhea. Twenty-two per cent of the patients stated that jaundice was the first symptom to attract attention. In 16 per cent the disease was ushered in by an upper respiratory infection and low grade fever. Eight per cent of the patients presented acute abdominal symptoms which caused them to be admitted on the surgical service. In 4 per cent right quadrant pain was the only prominent symptom at onset.

TABLE 1
Interval between onset of symptoms and appearance of jaundice

	NO. OF CASES	SYMPTOMS PRESENT	1-7 DAYS	8-14 DAYS	15 DAYS	1 MONTH	2 MONTHS	3 MONTHS	4 MONTHS	5 MONTHS	11 MONTHS
Infectious group.....	41	41	19	14	1	2	1	1	1	1	1
Post-plasma group.....	33	18	15	3	0	0	0	0	0	0	0

The duration of pre-icteric symptoms was recorded in 40 cases of infectious hepatitis and 33 cases of hepatitis following plasma. In the majority of the infectious group, the pre-icteric period varied from several days to two weeks (table 1). In 2 cases it lasted thirty days. In 4 other cases it was prolonged to two, four, five, and eleven months respectively (Cases 51, 91, 1, 19). In the plasma group, the most significant observation was the absence of pre-icteric symptoms in 15 cases. In these the usual symptoms of hepatitis became manifest simultaneously with or after the appearance of jaundice. In fifteen others the duration was a week or less and in the remaining three, one to two weeks. The average for this group was 4.9 days. When present, the symptoms were mild and attracted little attention, being elicited only on questioning. These plasma patients were hospitalized continuously since they were wounded and were not subject to physical exertion except that incident to transportation. Nine patients developed pre-icteric symptoms and jaundice while in transit or within two days after arrival.

Case 19. White soldier, age 23, $2\frac{3}{12}$ years service, admitted November 29, 1943. In January 1943, he began to have gastric intolerance to food, especially fats.

Subsequently he developed anorexia, weight loss, weakness and dizziness. During July and August nausea occurred after all meals and vomiting about once a week. In September he was admitted to a station hospital where blood studies including sedimentation rate, icterus index, and search for infectious mononucleosis were negative. On December 12, slight jaundice was noted and the icterus index rose to thirty. The liver was enlarged and tender. After remission of jaundice, the bromsulphthalein retention was 40 per cent at thirty minutes. After seven weeks hospitalization and hepatitis regimen, the dye excretion became normal, symptoms disappeared, weight increased 10 lbs., and liver decreased in size. He returned to duty three months after admission.

This case illustrates the existence of unrecognized hepatitis for eleven months prior to the appearance of jaundice. It remained unrecognized during his first hospitalization when hepatitis therapy was not employed. Improvement was prompt after institution of a hepatitis regimen.

TABLE 2
Symptoms of hepatitis

	ACUTE INFECTIONS	POST PLASMA	CHRONIC HEPATITIS	TOTAL
	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>	<i>per cent</i>
Anorexia.....	87	97	84	88
Nausea.....	90	89	80	88
Vomiting.....	78	67	69	74
Fat intolerance.....	78	80	90	81
Diarrhea.....	21	14	34	24
Fever.....	50	14	0	28
Pain.....	78	50	89	75
Fatigue.....	75	97	93	84
Pruritis.....	36	14	10	25
Liver tenderness.....	91	97	87	91
Liver enlargement.....	90	100	86	91
Enlarged spleen.....	9	8	7	8

Symptoms. The frequency of symptoms is indicated in table 2. The character of symptoms has been amply described elsewhere. In general it may be stated that the severity and persistence of symptoms depend upon factors not ordinarily encountered in civilian practice. These are mainly extreme fatigue, insufficient rest, and restricted or improper diet which is unavoidable in combat areas or under conditions of arduous military training. In many instances patients continued on duty for months in the presence of symptoms or even jaundice or received no hospitalization at all. Some patients failed to report for sick call because they believed their symptoms unimportant. The same conditions that caused increased morbidity were also responsible for recurrences among chronic cases. The mildest symptoms occurred in the post plasma cases who were under conditions of rest during the onset and course of the hepatitis.

Pain. Abdominal pain was usually located in the upper right quadrant or

epigastrium to the right of midline. It was most frequent in the chronic group and least in the plasma group. In some instances, particularly among the chronic cases, the pain resembled that of cholecystitis in character and radiation. Mistaken diagnoses of gall bladder disease were not uncommon.

Acute abdominal symptoms. In 14 cases of hepatitis, symptoms resembling an acute abdomen led to a surgical diagnosis. Of these, six were operated on and eight were transferred to the medical service after a diagnosis of hepatitis was established. In the former group, appendectomy was performed in four (Cases 21, 24, 25, 64), without finding an acutely inflamed appendix; in one other (137), acute cholecystitis was suspected; in one, intestinal obstruction (9). Three of the appendectomies were followed by jaundice within two to eleven days. The fourth appendectomy case was diagnosed as chronic hepatitis. The diagnosis of intestinal obstruction was made in a patient with hepatitis without jaundice in whom laparotomy did not disclose any pathology other than an enlarged liver. Case 137, suspected of acute cholecystitis, revealed a normal gall bladder.

In the non-operative group, the following diagnoses were made prior to the recognition of hepatitis; appendicitis 3, acute cholecystitis 1, intestinal obstruction 2, ruptured peptic ulcer 1, pelvic inflammatory disease 1.

Case 21. White male, age 20, one year service, admitted February 27, 1944. Past history negative. On January 22, 1944, he was operated on for suspected appendicitis. He made an uneventful recovery until January 30, when sutures were removed. On January 31, following a coughing attack, rupture of incision occurred with evisceration. Secondary closure was made under spinal anesthesia. On February 2 jaundice was noted for the first time. RBC 3.84; Hbg. 85 per cent; WBC 7,500; differential normal. Improvement was rapid. February 12; out of bed. February 19; scheduled for discharge. February 20; chill, weakness, and nausea. February 21; jaundice noted again, colicky pain in upper right quadrant. February 23; liver and spleen enlarged. Acute symptoms subsided February 27; transferred to this hospital. Patient ambulatory but weak, temperature normal; icterus index 58, RBC 3.68, Hbg. 75, WBC 6,900, sedimentation rate, prothrombin, urobilinogen normal. March 3, symptom free; icterus index 25. Bromsulphthalein 10 per cent, blood count moderate, serum protein, blood fragility, urobilinogen, prothrombin normal. Liver and spleen decreased in size and remained palpable for three months.

Case 24. White female, age 19, civilian dependent, admitted January 19, 1944. Symptoms consisted of lower right quadrant pain, fever, and vomiting. WBC 1,500; polynuclears 86 per cent. Operation performed and normal appendix removed. Jaundice appeared on fifth post operative day. Recovery was uneventful.

Case 64. (See under chronic hepatitis.)

Case 62. White male, age 27, $2\frac{2}{3}$ years service, admitted May 21, 1945, because of upper right quadrant pain radiating to the back. In November 1944, while overseas, he became jaundiced for six weeks with no symptoms other than anorexia. He was not hospitalized. In January 1945 he developed upper right quadrant pain associated with fat intolerance, fatigue, nausea and vomiting, and was hospitalized for fifty-nine days. He received a soft diet and bed rest; felt well during March and April while continuing diet. Upon resuming full diet symptoms returned; liver was only slightly enlarged, but very tender. Icterus index, bromsulphthalein, serum albumin, and globulin, NPN, urobilinogen, normal. Gall bladder failed to visualize after two attempts. Two additional failures of visualization were reported during previous hospitalization. Cholecystectomy was performed. Gall bladder was normal.

Diarrhea. Significant diarrhea was present in 24 per cent of cases in this series during the course of the disease (table 2). It was most frequent in the chronic group and least common among the plasma patients. It was usually intermittent. In some of the chronic cases, it was continuous since the onset of the acute stage. The diarrhea was usually associated with varying degrees of abdominal pain. There was no apparent relationship to liver function tests or other laboratory studies. While this symptom was attributed to the hepatitis, no definite explanation of its mechanism can be offered. Chemical analyses of the feces were not done. Stool cultures and search for parasites were negative. Gastric analysis and barium enema studies were normal; sigmoidoscopy did not reveal significant mucosal pathology.

Duration of jaundice in acute infectious and plasma cases. The period of jaundice was estimated from the date of the onset of jaundice to the date on which a normal icterus index was obtained. Accurate record was obtainable in 77 cases of infectious hepatitis and 33 cases of jaundice following plasma. In the infectious group, the duration ranged from 7 to 185 days with an average of 45 days. In the plasma group, the period of jaundice ranged from 15 to 80 days with an average of 36 days. In the infectious group, the longest periods of jaundice occurred in soldiers in whom treatment had been delayed or inadequate. Such patients were those who were in the field, on maneuvers, on restricted rations, and who failed to report to sick call until the jaundice was well advanced. Often such patients' recovery was delayed even after hospitalization because they were not placed on special diets; ate in the general mess, and bed rest was not enforced. Conversely, the shortest periods were observed in those patients who were not subjected to strenuous physical exertion and who were hospitalized early in their illness and who were subjected to strict hepatitis regimen. This was noted particularly in civilian dependents, detachment personnel, or prisoners of war attached to the post. These patients were not under conditions of physical hardship when symptoms appeared; were hospitalized promptly, and received carefully supervised hepatitis management.

The plasma group developed jaundice while in the hospital or within a few days after arrival. They were at complete rest from the onset and hepatitis routine was instituted immediately. These patients not only had milder symptoms, but recovered more rapidly.

Comparison of icterus index and bromsulphthalein in acute cases (2). In 16 cases of infectious hepatitis, followed by recovery, retention of bromsulphthalein was observed after return of the icterus index to a normal level. Ten per cent (3) or less of dye at thirty minutes (5 mg. per kilo) was considered normal (table 3). The degree of retention varied from 30 to 15 per cent. The duration of retention ranged from ten to 90 days after the disappearance of jaundice.

TABLE 3
Retention of bromsulphthalein in acute hepatitis after icterus index has become normal

CASE NO.	DURATION OF JAUNDICE	HIGHEST ICTERUS INDEX	BROMSULPHTHALEIN RETENTION	DURATION OF RETENTION
	days		per cent	days
34	105	125	30	75
79	100	150	15	15
82	36	59	20	30
84	8	13	28	16
108	23	44	24	14
123	78	30	25	30
130	30	80	30	21
133	40	104	20	15
177	22	62	20	90
194	20	23	15	17
111	14	16	25	14
14	18	23	25	15
162 (plasma)	30	47	20	30
182 (plasma)	22	30	20	15
183 (plasma)	44	45	22	15
200 (plasma)	24	71	20	10

There was no relationship between the degree of liver damage in these cases that recovered, and the degree or duration of jaundice. The longest period of liver dysfunction (90 days) occurred in a patient with a short period of jaundice, but who was ill for three weeks before hospitalization and who returned to duty before complete recovery.

Case 177. White male medical officer, age 41, was admitted to the hospital March 18, 1945, complaining of fatigue, upper right quadrant pain, and jaundice. For three weeks prior to admission, he was aware of malaise and occasional low grade fever but continued on duty. He sought admission after jaundice became apparent. The icterus index on admission was 42.5. There was a weight loss of 14 lbs. The liver was enlarged and tender. WBC 7,200; lymphocytes 46 per cent; other labora-

tory studies were within normal limits. Course of illness was uneventful. Patient insisted on leaving the hospital on May 10 when the icterus became normal (7.5); the bromsulphthalein showed 30 per cent retention and liver was slightly enlarged and tender. He was followed as an out patient. After ninety days, liver function became normal. The icterus index remained normal throughout; mild digestive symptoms were present during the three month period.

Persistence of elevated serum bilirubin with normal bromsulphthalein excretion. The retention of bromsulphthalein in the presence of jaundice is recognized. At the clinical disappearance of jaundice, bromsulphthalein determination was performed in addition to other laboratory examinations, which were done at

TABLE 4

Normal bromsulphthalein excretion in acute hepatitis prior to complete disappearance of jaundice

CASE NO.	DURATION OF JAUNDICE	HIGHEST ICTERUS INDEX	ICTERUS INDEX ON DAY OF FIRST NORMAL BSP	ELEVATED ICTERUS INDEX AFTER NORMAL BSP
	days			days
25	30	30	19	7
26	21	66	21	5
42	130	210	17	14
65	60	102	30	30
92	22	44	20	10
109	100	66	35	60
120	23	50	15	8
124	26	20	20	9
139	38	112	19	12
141	35	20	20	25
142 (plasma)	38	100	17	14
154 (plasma)	49	80	15	30
186 (plasma)	30	66	14	7
192 (plasma)	20	25	25	14
175 (plasma)	20	63	28	9

regular intervals. In 15 patients the icterus index remained elevated after the dye excretion became normal (table 4). Ten of these patients were ordinary infectious hepatitis and five were plasma cases. The time interval varied from 7 to 60 days.

There seemed to be no relationship between the degree of jaundice and the early attainment of normal bromsulphthalein function. No explanation is offered for the findings. However, it was noted that in the majority of cases, the duration of jaundice was below the average and the twelve of the fifteen cases were described as "mild" from the standpoint of symptoms and onset of jaundice was the only significant feature.

Acute hepatitis without jaundice. Hepatitis without jaundice is often a rela-

tive term. Faint jaundice, unnoticed by the patient, may exist prior to his coming under observation.

Five patients did not have associated jaundice. Four of them were under observation for other conditions, and the fifth was seen frequently by his dispensary surgeon, so that the absence of jaundice was certain. A characteristic onset and symptomatology were present in all. There was no history of previous liver damage. Recovery occurred in from one to three months. In one case hepatitis occurred in the course of infectious mononucleosis. In the others the onset did not differ from the usual type. The liver was enlarged and tender. The icterus index was normal. Bromsulphthalein retention was present in all. Cephalin flocculation was performed in 4 cases and was positive in two. Serum protein determination performed on three cases was normal. The diagnosis was based on a characteristic clinical picture with positive liver function tests which became normal with treatment.

Case 30. White nurse, age 24, who was under observation as an out patient, was admitted for study because of a progressive optic atrophy on April 3, 1944. Several days later she developed chill, fever (101°), anorexia, nausea and vomiting, and abdominal pain. For three weeks prior to admission, she had an intermittent diarrhea. The liver was enlarged three fingers below costal margin and tender. There was no visible jaundice; icterus index was 8; bromsulphthalein 25 per cent in thirty minutes, and 20 per cent in forty-five minutes. Sedimentation rate, 21 mm./hour. Blood count was normal with relative lymphocytosis. After four weeks of hepatitis regimen, bromsulphthalein excretion became normal and liver returned to normal size. There was a weight loss of 10 lbs.

CHRONIC HEPATITIS (TABLE 5)

Fifty-seven cases of chronic hepatitis were encountered in this series. Patients who had symptoms for a period longer than six months were classified as chronic. For purposes of discussion, the cases were divided into five groups: 1. Those with symptoms which were continuous since the initial attack of jaundice. 2. Those with recurrent symptoms associated with recurrent jaundice. 3. Those with recurrent symptoms but without repetition of jaundice since the first attack. 4. Those without any evidence of jaundice at any time during the course of the hepatitis. 5. Those in whom persistent symptoms were attributed to psychoneurosis.

Group 1. Continuous symptoms. There were ten patients in this group. The time interval since the initial onset of jaundice varied from 7 to 27 months. Jaundice was not present in any patient during the period of observation. In seven patients the initial jaundice was attributed to infectious hepatitis and in three it followed the giving of yellow fever vaccine. Recurrent jaundice was noted in only one patient (Case 67). The symptoms were similar to those found during the acute stage. Enlarged liver in varying degree; liver tender-

TABLE 5
Chronic hepatitis—Summary of findings in 57 cases

CASE NO.	GROUP	INTER- VAL SINCE INITIAL JAUN- DICE	RECUR- RENT JAUN- DICE	TENDER EN- LARGED LIVER	LIVER FUNCTION TESTS	PAIN	DIAR- RHEA	DYSPEP- SIA	WEIGHT LOSS	VACCINE OR HEPATITIS
		<i>years</i>							<i>lbs.</i>	
1	I	$\frac{6}{1\frac{1}{2}}$	0	+	+ BSP	+	0	+	+	Hep.
10	I	$\frac{7}{1\frac{1}{2}}$	0	+	0	+	+	+	15	Hep.
32	I	$\frac{7}{1\frac{1}{2}}$	0	+	0	+	0	+	18	Hep.
47	I	$\frac{8}{1\frac{1}{2}}$	0	+	0	+	0	+	16	Hep.
55	I	$\frac{7}{1\frac{1}{2}}$	0	+	0	+	0	+	20	Hep.
67	I	$\frac{7}{1\frac{1}{2}}$	+	+	+ BSP	+	0	+	0	Vacc.
70	I	$\frac{11\frac{6}{12}}{1\frac{1}{2}}$	0	0	0	+	+	+	0	Vacc.
73	I	$\frac{2\frac{3}{4}}{1\frac{1}{2}}$	0	+	0	+	0	+	40	Vacc.
118	I	$\frac{7}{1\frac{1}{2}}$	0	+	0	+	0	+	0	Hep.
166	I	$\frac{7}{1\frac{1}{2}}$	0	+	+ BSP	+	+	+	20	Hep.
53	II	$\frac{9}{1\frac{1}{2}}$	+	+	0	+	0	+	10	Hep.
59	II	$\frac{1\frac{4}{12}}{1\frac{1}{2}}$	+	+	0	+	0	+	—	Hep. & Vacc.
64	II	$\frac{2\frac{8}{12}}{1\frac{1}{2}}$	+	0	0	+	+	+	50	Vacc.
74	II	$\frac{2\frac{1}{12}}{1\frac{1}{2}}$	+	+	+ CF	+	0	+	+	Hep.
69	II	3	+	+	0	+	+	+	51	Vacc. & Hep.
81	II	$\frac{2\frac{4}{12}}{1\frac{1}{2}}$	+	+	0	+	+	+	30	Vacc.
83	II	$\frac{1\frac{4}{12}}{1\frac{1}{2}}$	+	+	0	+	+	0	15	Hep.
93	II	7	+	+	+ BSP	+	+	+	0	Hep.
95	II	7	+	+	0	+	0	+	0	Hep.
100	II	$\frac{2\frac{6}{12}}{1\frac{1}{2}}$	+	+	+ AG	+	0	+	—	Hep.
101	II	13	+	+	+ AG	+	0	+	0	Hep.
102	II	19	+	+	+ AG, CF	+	+	+	35	Vacc.
117	II	10	+	+	+ BSP	+	+	+	+	Hep.
122	II	9	+	+	+ BSP, CF, AG	+	0	+	27	Hep.
171	II	$\frac{1\frac{4}{12}}{1\frac{1}{2}}$	+	+	0	+	0	+	12	Hep.
191	II	$\frac{3\frac{2}{12}}{1\frac{1}{2}}$	+	+	0	+	+	+	78	Vacc.
198	II	$\frac{1\frac{8}{12}}{1\frac{1}{2}}$	+	+	0	+	0	+	—	Hep.
2	III	$\frac{8}{1\frac{1}{2}}$	0	0	0	+	+	+	+	Hep.
3	III	2	0	+	0	+	0	+	20	Vacc.
7	III	5	0	+	+ BSP	+	0	+	—	Hep.
17	III	2	0	0	0	+	0	+	21	Vacc.
20	III	1	0	+	0	+	+	+	20	Vacc.
39	III	$\frac{8}{1\frac{1}{2}}$	0	+	0	+	0	+	20	Hep.
72	III	1	0	+	+ CF	+	0	+	36	Hep.
76	III	$\frac{9}{1\frac{1}{2}}$	0	+	0	+	+	+	10	Hep.
77	III	3	0	+	0	+	+	+	0	Hep.
86	III	2	0	+	0	+	+	+	+	Vacc.
94	III	2	0	+	0	0	0	0	14	Vacc.
98	III	2	0	+	0	0	0	+	20	Vacc.

TABLE 5—Continued

CASE NO.	GROUP	INTER- VAL SINCE INITIAL JAUN- DICE	RECUR- RENT JAUN- DICE	TENDER EN- LARGED LIVER	LIVER FUNCTION TESTS	PAIN	DIAR- RHEA	DYSPEP- SIA	WEIGHT LOSS	VACCINE OR HEPATITIS
		years							lbs.	
114	III	2 $\frac{1}{2}$	0	+	+ AG	0	0	+	30	Vacc.
136	III	12	0	+	0	+	0	+	0	Hep.
140	III	$\frac{9}{12}$	0	+	0	+	0	+	15	Hep.
143	III	2 $\frac{1}{2}$	0	+	0	+	0	+	0	Hep.
179	III	1 $\frac{5}{12}$	0	+	0	+	+	+	—	Hep.
180	III	$\frac{7}{12}$	0	+	+ BSP	0	0	+	—	Hep.
190	III	3 $\frac{5}{12}$	0	+	+ BSP, CF	+	0	+	0	Hep.
195	III	$\frac{11}{12}$	0	+	+ CF	+	0	+	0	Hep.
62	III	$\frac{7}{12}$	0	0	0	+	0	+	20	Hep.
56	III	24	0	+	0	+	+	+	0	Hep.
9	IV	1 $\frac{8}{12}$	0	+	+ BSP	+	+	+	30	Hep.
50	IV	$\frac{7}{12}$	0	+	0	+	0	+	35	Hep.
88	IV	2	0	+	+ BSP, CF	+	0	+	0	Hep.
44	V	2 $\frac{2}{12}$	0	0	0	+	0	+	0	Vacc.
87	V	2 $\frac{2}{12}$	0	0	0	+	+	+	10	Vacc.
107	V	$\frac{8}{12}$	0	0	0	+	0	+	0	Hep.
138	V	$\frac{8}{12}$	0	0	0	+	0	+	14	Hep.
167	V	2 $\frac{9}{12}$	0	0	0	0	0	+	18	Vacc.

Symbols: BSP—Bromsulphthalein.

CF—Cephaline Flocculation.

AG—Albumen Globulin Ratio.

ness, upper right quadrant pain, and dyspepsia were present in all. Intermittent diarrhea was present in four, and weight loss from sixteen to forty pounds was noted in seven. Weakness was the most prominent symptom in some. Bromsulphthalein retention was present in three. The character of symptoms and physical findings in those with liver dysfunction differed in no way from those in whom liver function was normal. Failure to recover from the acute attack was attributed to insufficient hospitalization; no hospitalization at all in one instance; too early return to full duty, and inability to obtain proper diet after discharge from hospital. The initial episode of jaundice occurred after entering military service in all patients in this group.

Case 32. White male, age 23, 3 $\frac{2}{12}$ years service, was admitted July 23, 1944. While overseas he began to have epigastric distress after meals, burning sensation and intolerance to fatty foods. He received no treatment and continued on combat duty. In January 1944 he observed the onset of anorexia, nausea and vomiting. On February 2, 1944, he developed a chill with low grade fever of four days duration; upper right quadrant pain, and mild jaundice. The highest icterus index during

this period was twenty-one. Diarrhea persisted for two weeks. He was hospitalized for five weeks after which he was started on an exercise tolerance course. With this program he observed marked fatigue and upper right quadrant pain. He was returned to bed at which time he was told that his liver was enlarged again. On May 15 he received another trial of exercise but had a recurrence of symptoms. He was then evacuated to the zone of the interior. Upon admission to this hospital, the outstanding symptoms were anorexia, nausea, upper right quadrant pain and weight loss of 18 lbs. The liver was enlarged and tender. Icterus index and bromsulphthalein, serum albumin and globulin, gastrointestinal and gall bladder x-rays were normal. With bed rest and diet he became symptom free and the liver returned to normal size.

Case 70. White male, officer, admitted July 20, 1944. He received yellow fever vaccine in February 1942 and developed jaundice in August 1942. Since then he had continuous anorexia, nausea, and intolerance to fatty foods. He had periodic upper right quadrant pain, weakness, and intermittent diarrhea which became pronounced with indulgence in food of a fatty character. The liver was not enlarged. Liver function studies, stool examinations, and x-ray studies were negative. Sigmoidoscopy showed a catarrhal mucosa. Patient improved with bed rest and diet.

Case 73. White male, age 27, $3\frac{1}{2}$ years service, admitted August 4, 1944. In February 1942 he received yellow fever vaccine. In May 1942 he developed dyspepsia and weakness three weeks before hospitalization. He was hospitalized for three weeks and then returned to duty. Following his hospitalization, he complained of continuous epigastric distress, nausea, intolerance of fatty foods with intermittent upper right quadrant pain and weakness. Upon admission, liver was enlarged and tender; weight loss 40 lbs. Liver function studies and x-ray examinations were normal. He improved with treatment and liver decreased in size.

The diagnosis in Case 70 may be questioned because of the absence of liver enlargement at the time of examination. The symptoms were characteristic. The diarrhea was not due to irritable colon. There was no evidence of neurosis, and response to treatment was prompt.

Group 2. Recurrent symptoms with recurrent jaundice. Seventeen patients were included in this group. All of these patients had two or more episodes of jaundice during the course of hepatitis. The time interval since the initial attack of jaundice ranged from 9 months to 10 years and averaged 61 months. Here also the symptoms differed little in character from those of the acute stage, or Group 1; upper right quadrant pain was present in all patients during recurrences. Dyspeptic symptoms such as anorexia, post prandial distress, intolerance to fats, and nausea were noted in all but one patient. Diarrhea not attributable to any known cause occurred intermittently in eight cases

Weight loss was significant, being present in eleven of fourteen cases in which it was recorded (78 per cent), averaging 34 lbs. and varying from ten to seventy-eight pounds. Appreciable enlargement of the liver associated with tenderness was present in all but one case (64). Hematemesis history was present in two cases (81 & 102). Evidence of liver dysfunction was observed in seven cases as indicated by bromsulphthalein, cephalin flocculation, albumin globulin ratio and urobilinogen.

Relationship of chronic hepatitis to army service. In eight patients the first attack of jaundice occurred at varying intervals prior to army service (Cases 59, 74, 93, 95, 101, 102, 122, 198). Of these, three patients had additional attacks of jaundice following the administration of yellow fever vaccine in 1942; three, four, and six months respectively (Cases 59, 95, 102). In eight other patients, the initial jaundice occurred after induction; four were attributed to infectious hepatitis and four followed yellow fever vaccine. One patient was a civilian dependent who had repeated incidents of jaundice prior to admission (Case 117).

Case 59. White medical officer, age 41, $1\frac{8}{12}$ years service, admitted January 3, 1943, as an evacuee from overseas because of recurrence of hepatitis symptoms and with a transfer diagnosis of psychoneurosis. In June 1942, he was hospitalized for four weeks because of jaundice which followed administration of yellow fever vaccine in March 1942. Previous episodes of jaundice occurred in 1926, 1927, and 1937. Periodic symptoms of hepatitis occurred prior to army service. Chief complaint on admission was weakness associated with upper right quadrant pain, and dyspepsia. The liver was moderately enlarged and tender. Laboratory examinations including x-ray and liver function studies were negative. Psychiatric consultant found no evidence of psychoneurosis.

Case 64. White male, battalion commander, age 35, admitted July 13, 1945, to the surgical service because of right sided abdominal pain for which an appendectomy was performed with the removal of a normal appendix. During convalescence from the operation, it was discovered that the liver was enlarged and tender and a history of hepatitis was obtained. In March 1942, he received yellow fever vaccine. In the early part of June 1942, he developed severe diarrhea for one week for which he was hospitalized for several weeks. Stool examinations revealed no amebiasis or bacillary dysentery. Shortly after discharge from the hospital, he developed jaundice which lasted thirty days. He continued on duty without hospitalization. Thereafter, he had continuous fatigue, anorexia, upper right quadrant pain, intolerance to fats and a total weight loss of 50 lbs. In March 1944, he had an exacerbation of symptoms with mild jaundice (icterus index 28). Hospitalization in March disclosed "no organic disease" other than the jaundice. Laboratory studies including liver function during recent admission were negative.

Case 83. White adult male, age 21, 3 years service, admitted January 25, 1945, for determination of physical status following termination of limited duty period.

First attack of jaundice in June 1943 when he was hospitalized for three weeks and returned to duty. He felt well until October 1943 when he noted upper right quadrant pain and was hospitalized with a presumptive diagnosis of appendicitis. During this hospitalization, jaundice was noted (icterus index 22). He was discharged after three weeks. In December 1943, he was hospitalized for two weeks because of upper respiratory infection and low grade jaundice was observed again. In February 1944, during check of physical condition, jaundice was noted again. He spent the next three months at an air corps convalescent center where an occasional elevation of icterus index was noted. He returned to duty in May 1944 and was symptom free. Examination in August 1944 revealed no complaints; moderately enlarged liver, and normal liver function tests. On the January 25, 1945, admission the chief complaints were excessive fatigue and upper right quadrant pain. The liver was enlarged two fingers below costal margin and tender. Icterus index was 25 and liver function tests were normal.

Case 93. White male, age 21, $1\frac{8}{12}$ years service, admitted September 19, 1944, because of upper right quadrant pain and mild jaundice. In 1937 he had an attack of upper right quadrant pain radiating to scapula, associated with nausea and vomiting, but was not aware of jaundice. In 1939 and 1940, repeated similar attacks plus intolerance to fats, fatigue, and diarrhea occurred. Diagnosis of cholecystitis was made. Another attack in 1941 was more severe and accompanied by clay colored stools. Since then; repeated and more frequent incidents of mild jaundice. Fatigue was prominent. Findings on admission; liver enlarged and tender, icterus index 22, bromsulphthalein 15% at thirty minutes, cephalin flocculation, serum protein, urobilinogen were normal.

Case 117. Female dependent, white, age 29, admitted October 22, 1944. Upper right quadrant pain radiating to scapula, and jaundice. In 1915 at age of twelve, she had upper abdominal pain and vomiting associated with faint icterus. During the next seven years she had intermittent nausea, fatigue, intolerance to fats, and right sided abdominal pain which led to suspicion of appendicitis. In 1934 she was jaundiced for two months. Cholecystitis was diagnosed and surgery advised. In 1936 and 1941 exacerbations of jaundice and upper right quadrant pain associated with abnormal gall bladder visualization led to recommendation of gall bladder surgery at two clinics. Attack on admission in October 1944 followed eating pork sausage. Jaundice was present; liver was enlarged to umbilicus, icterus index 20, bromsulphthalein retention after jaundice subsided, 35 per cent. Other liver function tests normal. Cholecystography normal. After six weeks treatment, patient became symptom free, liver was reduced in size, icterus index and bromsulphthalein normal. Hemolytic jaundice was excluded. She continued on ambulatory treatment for one year. Check examinations in June and October 1945 showed normal size liver, normal liver function, gain of 15 lbs. and freedom of symptoms.

Case 122. Colored male, age 30, $3\frac{8}{12}$ years service, admitted November 16, 1944. In 1935; jaundice of three weeks duration. Since 1940, had gastrointestinal

symptoms. March 1944; hospitalized at a station hospital for upper abdominal pain suspected of ulcer, and discharged with a diagnosis of gastritis. He continued on duty until jaundice supervened in August 1944 and was hospitalized at his station. On admission to this hospital, liver was moderately enlarged, icterus index 23, serum albumin 3.5, globulin 4, cephalin 4+, x-rays of stomach and gall bladder normal. Improved on treatment, jaundice receded, and serum protein became normal on December 3, 1944. Bromsulphthalein, December 3, 1944, 32 per cent. February 3, 1945, peritoneoscopy with liver biopsy. Pathologist could not find sufficient evidence for diagnosis of cirrhosis and made a diagnosis of proliferative hepatitis.

Case 191. White officer, age 34, 4 years service, admitted May 30, 1945. Chief complaint, upper right quadrant pain with vomiting. January 1942; yellow fever vaccine. February 1942; hospitalized two weeks because of epigastric pain, bloating and jaundice. X-ray of stomach and gall bladder negative. Returned to duty but felt weak and had upper abdominal pain. In January to May 1943; hospitalized overseas four times for two week periods because of recurrent upper right quadrant pain, nausea, and vomiting. Patient not certain about jaundice during this period. During this time also had rectal bleeding; hemorrhoidectomy was considered. From January to June 1944, patient's weight dropped from 235 lbs. to 165 lbs. and he experienced upper right quadrant pain, vomiting, and intermittent diarrhea. In July 1944, he returned to the United States; felt better, and regained up to 200 lbs. In November 1944 while overseas again, he again developed vomiting and diarrhea but was not hospitalized. December 1944; treated in quarters for weakness and diarrhea of undetermined origin. January 1945; jaundice and enlarged liver were noted, when he was hospitalized for five weeks and received five units of plasma. During this period weight dropped from 200 lbs. to 165 lbs. February 5, 1945; returned to duty but hospitalized again on February 20. Anemia was noted; blood transfusion given. Weight loss continued to 130 lbs. Through chain of evacuation, he arrived at this hospital. On admission, weight was 150 lbs., liver enlarged to umbilicus and tender. Icterus index and liver function tests normal. After three months liver receded. Symptoms disappeared; weight increased. After two additional months of sick leave, liver was normal in size.

Group 3. Recurrent symptoms without jaundice. Twenty-two patients with chronic hepatitis had recurrent symptoms without associated recurrence of jaundice. The clinical picture did not differ in character materially from those in Group 2. The time interval since the initial jaundice was shorter, varying from 8 months to 12 years with an average duration of 20 months. Upper right quadrant pain was present in 18 cases (82%), dyspeptic symptoms in all but one, diarrhea only in seven (32%), weight loss in thirteen of eighteen recorded cases (72%), averaging 20 lbs., liver enlargement and tenderness in nineteen (86%), positive liver function tests in six (27%). In seven cases, the initial jaundice followed the administration of yellow fever vaccine and in 15 cases, infectious hepatitis.

Relationship to army service: In this group, twenty-one were soldiers and one a civilian dependent. Among the 21 cases, fifteen (71%) had the initial attack of jaundice during army service; eight were considered infectious hepatitis, and in seven the jaundice followed yellow fever vaccine. In six cases the initial jaundice antedated induction. In the civilian, the jaundice was associated with infectious mononucleosis.

As additional factors contributing to chronicity may be mentioned a significant history of malaria in 6 cases and complete failure of previous hospitalization during the acute stage in 3 cases. A period of ascitis occurred in two cases (72, 76) in whom the hepatitis had existed for twelve and nine months respectively, but fluid was not found during the recent hospitalization.

Case 72. White male, age 19, one year service, was admitted July 28, 1944. He developed hepatitis with jaundice in August 1943. This was preceded by one month of diarrhea, vomiting and abdominal pain. In September 1943, a period of ascitis intervened. He was discharged to duty in November 1943 after four months hospitalization. In December 1943, there was a recurrence of fatigue, upper right quadrant pain, anorexia, and fat intolerance. The same symptoms were present on admission. The liver was enlarged and tender. Icterus index, bromsulphthalein and serum albumin and globulin were normal. Cephalin flocculation, 3+.

Case 140. Female, civilian, age 35, admitted December 18, 1944, because of upper right quadrant pain, nausea, and vomiting. In February 1944, patient developed jaundice of one week's duration in the course of infectious mononucleosis. She was hospitalized for four weeks. Since then she had recurrent symptoms of hepatitis with attacks of upper right quadrant pain which led to a diagnosis of cholecystitis and recommendation of surgery. Liver was enlarged and tender; liver function tests were normal. Cholecystography showed normal visualization. After two months hospitalization, patient became symptom free and liver receded to normal size.

This case illustrates the development of chronic hepatitis after comparatively mild jaundice which was considered a "complication" of infectious mononucleosis. Little importance was attached to the transient jaundice and patient was not cautioned to follow a hepatitis regimen, the observance of which may have prevented recurrence. The upper right quadrant pain was mistakenly attributed to gall bladder disease. Hepatitis may follow infectious mononucleosis without jaundice.

Case 179. White male officer, age 26, admitted April 10, 1945. Patient was jaundiced three weeks in December 1943 while overseas. He was not hospitalized but was advised to follow a hepatitis type of diet, which was impossible. For one month after the jaundice, he continued to have upper right quadrant pain, occasional nausea and vomiting, and distress after greasy food. He continued on combat duty; felt better during the summer of 1944, but had a recurrence of severe upper right quadrant pain and nausea without jaundice in September 1944. He was evacuated to continental United States, feeling better during the course of evacuation.

While home on leave, another recurrence followed overindulgence in rich food. On admission, liver was enlarged and tender; liver function tests normal.

Case 62. White male, age 27, admitted May 21, 1945. In November 1944, he became jaundiced; remained so for six weeks, but was not hospitalized. He had no symptoms other than anorexia during the jaundice and until January 1945 when he developed upper right quadrant pain and intolerance to fats and was hospitalized for 59 days. During hospitalization, gall bladder visualization failed on two attempts. He felt well during March and April when he observed dietary restrictions. Upon resuming ordinary diet symptoms returned and he was re-hospitalized May 21. Two additional cholecystographies, one of which was intravenous, failed to visualize the gall bladder. Liver function tests were normal. Liver was slightly enlarged but tender. Laparotomy disclosed a normal gall bladder.

This case, as some of the others above, illustrates the failure of gall bladder visualization during the presence of symptoms a long time after the acute attack in spite of the normal icterus index and normal excretion of bromsulphthalein.

Case 56. White male dental officer, age 39, admitted February 24, 1945. Chief complaints; weakness, vague joint pains and intermittent diarrhea. At age of 15, he had jaundice of four weeks duration. During the next five years he had repeated attacks of malaria. Physical examination showed moderate obesity and liver enlarged to umbilicus with sharp edge. All laboratory studies and liver function tests including icterus index were normal. The gall bladder failed to visualize after two attempts; similar failure of cholecystography during a hospitalization six months previously. Hepatitis regimen produced considerable improvement and decrease in size of liver. Laparotomy May 2, 1945, showed normal size liver, normal gall bladder; a chronic appendix was removed.

Microscopic study of biopsy section of liver showed distortion of the architecture of the liver. The capsule was thickened and a broad connective tissue layer covered the parenchyma. Within this layer there was a moderate proliferation of bile ducts and considerable infiltration predominated by lymphocytes. In the parenchyma were seen large masses of liver cells, frequently with fatty vacuolations, but without the usual lobular architecture. There was a very moderate excess of fibrous tissue, principally in relation to some of the portal spaces. This fibrosis was not marked. The striking feature, apart from the loss of architecture, was the extensive cellular infiltration consisting predominately of lymphocytes and very numerous plasma cells, together with scattered polynuclears. These cells were present around recognizable portal spaces, and in addition were seen around some of the central veins as well as in small foci indiscriminately through the parenchyma. There was no bile stasis.

The pathologist could not make a definite tissue diagnosis and used the term proliferative hepatitis. This picture was not that of portal or biliary cirrhosis nor did it resemble the acute or healing stage of acute hepatitis.

In September 1945 he was readmitted because of recurrence of symptoms, liver tenderness and enlargement of three fingers below costal margin.

Group 4. Three patients with a syndrome of chronic hepatitis had no evidence of clinical jaundice or elevation of serum bilirubin during the entire course of the disease. The duration was twenty, seven, and twenty-four months. All three had recurrences of symptoms after attempts at duty which were associated with liver enlargement and tenderness. Bromsulphthalein retention was present in two. In the third, all liver function tests were negative at the time of observation but the cephalin flocculation was 4+ repeatedly during previous hospitalization.

Case 9. White nurse, age 24, admitted November 15, 1943, with complaints of abdominal pain, distention, diarrhea, nausea, and vomiting. Prior to entering the hospital, she had unexplained diarrhea from July 15 to August 6, 1943. The liver was enlarged and tender. All laboratory studies were negative except bromsulphthalein retention of 32 per cent at thirty minutes. After two months, patient improved sufficiently to be transferred to a hospital nearer her home for convalescence on January 26, 1944. There, the abdominal symptoms, particularly the distention, again became acute. A tentative diagnosis of intestinal obstruction was made. Laparotomy failed to reveal any evidence of obstruction. Following recovery from the operation, she left the hospital for a convalescent leave, but had to return three days later because of recurrent upper right quadrant pain. From June 1944 to June 1945, patient's attempt to perform duty was interrupted by hospitalizations due to recurrence of nausea, upper right quadrant pain, and weight loss, in spite of improvement while in hospital. The liver varied in size but remained enlarged. Bromsulphthalein retention varied from 20 to 30 per cent. She was discharged from the army in July 1945 with persistent mild symptoms and normal bromsulphthalein excretion. Icterus index was not elevated at any time since the onset.

Group 5. Psychoneurosis. In five patients complaining of persistent symptoms of chronic hepatitis, a diagnosis of psychoneurosis was made. Such a diagnosis is obviously difficult to establish in a disease in which symptoms may exist without positive laboratory evidence (5). In addition to negative liver function tests and absence of physical findings, these patients failed to show any improvement after persistent therapeutic trials. Liver enlargement or tenderness was absent in all. Dyspepsia was present in all and occasional diarrhea in one. In three cases, the initial jaundice followed yellow fever vaccine and in two was associated with infectious hepatitis. The duration of symptoms varied from 8 months to $2\frac{9}{12}$ years.

Symptomatology. The symptoms of chronic hepatitis resemble in character those of the acute stage. Comparison of the groups of cases noted above reveals that the symptomatology does not vary whether the symptoms are continuous or intermittent, with or without recurrent jaundice, with infectious or post vaccinal type. Nor does the duration alter the symptoms appreciably with each recurrence. The predominant features are digestive symptoms,

characterized by nausea, anorexia, post prandial distress with intolerance to fats; upper right quadrant or epigastric pain; fatigue, weight loss. Diarrhea not attributable to any other cause occurs frequently. The liver is almost always enlarged and tender. Recurrences are more frequently unassociated with repeated jaundice. Jaundice may be absent even with the initial attack of hepatitis or may be so insignificant that it may be unobserved by the patient or physician. The upper right quadrant pain may resemble biliary colic and be particularly misleading when accompanied by jaundice or by failure of visualization during an isolated cholecystography. Marked chronicity is a prominent feature.

Diagnosis. The diagnosis of chronic hepatitis depends largely upon the history plus the presence of tenderness and enlargement of the liver. The presence of positive liver function tests and jaundice are helpful but their absence does not rule out such a diagnosis. Serial liver function determinations are of course more helpful than single examinations. Of additional value is information concerning liver function during previous attacks. The most valuable single test is the bromsulphthalein one. The exclusion of other disease is of course essential. Vague symptoms unsupported by positive laboratory data may lead to the erroneous impression of neurosis. Careful history will distinguish the recurrent jaundice of chronic hepatitis from acute hepatitis during an epidemic.

Treatment by diet and bed rest must be prolonged; requiring many months in some instances. Bed rest is essential and hospitalization preferable when possible. The criteria for improvement are disappearance of symptoms, gain in weight, reduction of liver to normal size, and re-establishment of normal liver function tests. Careful and thorough treatment of the initial attack will prevent recurrences and chronicity. The remission of jaundice is not to be regarded as synonymous with cure. Our diet included 2600 calories in the form of three meals high in protein and carbohydrates and low in fat (40 grams) and an additional 1000 calories in the form of a "hepatitis mixture" taken between meals, plus supplemental vitamins.

Success of treatment depends not only upon careful and persistent treatment, but also upon the early recognition of the disease, when symptoms are mild, and prompt hospitalization. In the group of plasma patients not a single recurrence of symptoms or jaundice occurred during a period of $1\frac{1}{2}$ years after their return to the surgical service. This is true in spite of the fact that following transfer from the medical service they resumed ordinary diet and were not subjected to restrictions of physical activity or alcohol. This does not imply that hepatitis following plasma is a mild disease. During the time interval from which this series was drawn, the only two fatalities from hepatitis were two plasma jaundice patients who arrived from overseas with extensive wounds, infection, and malnutrition.

SUMMARY

A series of 200 cases of hepatitis was analyzed. The character of onset was variable. Pre-icteric symptoms were of shortest duration in patients not subjected to strenuous physical exertion and dietary restrictions and were frequently absent in those at rest. In the acute cases the symptoms during the course of the disease were mildest and of shortest duration in patients who were hospitalized early and who were not subjected to prolonged fatigue. This was particularly true of the plasma cases. In some instances an erroneous diagnosis of acute abdomen was made. Evidence of liver dysfunction may persist for a variable period following the disappearance of jaundice in acute hepatitis. Severe hepatitis which in some cases became chronic occurred in some of the patients without the development of jaundice at any time. Chronic hepatitis was encountered with or without recurrent jaundice after the initial attack. Symptoms were continuous or recurrent. Positive liver function tests were considered of diagnostic aid but not essential. The diagnosis was based on the recurrence of characteristic symptoms with a previous attack of acute hepatitis and an enlargement and tenderness of the liver. Treatment must be persistent and bed rest imperative in both acute and chronic cases. Early and careful treatment of acute cases will prevent chronicity. In chronic cases the results of treatment are good but recurrence must be anticipated in some instances.

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CHRONIC RELAPSING PANCREATITIS

A STUDY OF TWENTY-NINE CASES WITHOUT ASSOCIATED DISEASE OF THE BILIARY OR GASTRO-INTESTINAL TRACT

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(Continued from April Issue)

ANALYSIS OF CASES

Incidence. Sex.—Of the twenty-nine patients, twenty-five (86 per cent) were male and four were female, a ratio of 6.2 males to 1.0 females. This sex incidence is in contradistinction to that observed in cases of cholecystic disease, in which females are predominantly affected.

Age at onset.—The youngest age at which pancreatitis apparently was manifest was ten years and the oldest sixty-six years. Four patients were less than twenty years of age and ten were less than thirty years of age when the disease first appeared. Thus pancreatitis may appear at a younger age than does cholecystic disease in the usual case. However, the mean age of onset was 38.3 years and the median age 37.0 years.

Family history.—The only suggestion of a possible familial incidence is in case 24, the patient stating that two sisters and a daughter had similar attacks of pain. These relatives have not been examined at the clinic.

Type of individual.—As a group, these patients were not obese, such as one might expect were one dealing with cholecystic disease. In twenty-two cases in which complete data were available, the average weight at the onset of disease was 159 pounds (72.1 kg.), which was only 4.7 pounds (2.1 kg.) more than the standard weight.

Possible etiologic factors. Alcohol.—Alcohol was used in seventeen (68 per cent) of the twenty-five cases in which such data were available. It was used heavily in eight cases (32 per cent), often over a period of several years. In cases 9, 11, 13 and 14 alcohol appeared to be a provocative factor in the painful attacks. The possible etiologic rôle of alcoholism in cases of pancreatitis has been stressed by various writers, among whom are Weiner and Tennant (1), Myers and Keefer (2) and Clark (3). In necropsy studies Weiner and Tennant noted chronic pancreatitis in 47 per cent of forty-one cases of chronic alcoholism. Myers and Keefer, also studying necropsy material, noted that alcoholism was an associated factor in a third of fifty-one cases of pancreatitis and in twenty-four cases in which there was fat necrosis. In 150 consecutive necropsies in cases of acute and chronic alcoholism Clark observed twenty-seven cases of pancreatitis.

Giardia.—*Giardia lamblia* could possibly have been a factor in the causation of pancreatitis in case 3, inasmuch as this organism was found in the gallbladder at the time of cholecystectomy, when pancreatitis was noted. We doubt whether *Giardia* was a factor in this case, however, since the attacks of pain continued after cholecystectomy and eradication of *Giardia* infection by the use of atabrine. Moreover, the diarrhea which was present before operation cleared after the foregoing treatment.

Trauma.—With the exception of case 21, trauma did not seem to be important as an original etiologic factor. In that case the first painful seizure occurred while the patient was playing baseball. Once the disease had appeared, unusual exertion and overwork were given as precipitating factors in the subsequent painful seizures in cases 3, 12, 14 and 17.

Infection.—Cultures of bile from the gallbladder or common bile duct, made in four cases at the time of operation, were positive in one case. In case 25 gram-negative bacilli were cultured in bile from the common duct. We doubt whether this infection was of any real etiologic significance.

The early manifestations of pancreatitis. **Pain.**—Typically and most frequently, pancreatitis begins with an acute and severe painful seizure. The onset was of this type in fourteen of the twenty-nine cases in this series (cases 2, 3, 6, 7, 10, 11, 12, 13, 17, 19, 21, 22, 24 and 28). However, the pain is not always typical or severe. Thus, in case 25 pain had never been severe and in case 27 there was a constant mild pain of a burning type in the right upper quadrant of the abdomen for two years prior to the first severe attack. In case 18 there was pain of the ulcer type for two years before the first severe painful seizure.

Pain and dyspepsia.—A minor type of pain and dyspepsia of the flatulent type occurred for one year in case 4 and for nine years in case 14 before the first severe seizure.

Dyspepsia alone.—Fairly frequently, dyspepsia of the flatulent type, together with intolerance to fatty foods without pain of any type, may be noted for long periods (one to seventeen years) before the first attack of severe pain (cases 1, 4, 5, 9 and 23). It is not certain that pancreatitis has been responsible for the dyspepsia.

Diarrhea.—In case 26, diarrhea preceded the attack of pain by a few days. In case 29, diarrhea (steatorrhea) was present two years before the first and only attack of pain.

Diabetes.—Case 29 was also unusual in that diabetes had been present three years before the onset of steatorrhea and for five years before the first attack of abdominal pain.

Hematemesis.—In case 8, gross hematemesis occurred eleven years before and again one year after the first painful seizure. In both instances it occurred in connection with the ingestion of an alcoholic drink by a man who used alco-

hol chronically. Although the exact cause for bleeding is speculative, it may well have been alcoholic gastritis. Walton and associates (4) reported the occurrence of gross gastro-intestinal hemorrhage in cases in which no lesion other than pancreatitis was found to explain the hemorrhage.

Seizures of pain. Number of years during which seizures of pain occurred.—The shortest period was two days, the longest twenty years and the average 5.7 years. It is important to note that seizures of pain occurred for five to ten years in sixteen cases and for ten years or longer in four cases.

Number of years during which attacks of pain occurred before the diagnosis was made.—The average period from the onset of seizures of pain until the diagnosis was made (twenty-seven cases) was 4.8 years. However, in more than a third of the cases a period of five years or more, and in one case nineteen years, had elapsed before the correct diagnosis was made.

Precipitating factors.—Food was mentioned in five cases as a provocative factor, alcohol in four cases, fatigue and exercise in eight cases and nervous and emotional stress in three cases. In some of these cases two or more of these factors were mentioned as apparent inciting agents.

Mode of onset and cessation.—In twenty of the twenty-nine cases the mode of onset was not stated. In four cases the onset was abrupt and in four cases the onset and development of pain were gradual. In one case the onset was given as either gradual or abrupt. In six cases there was gradual cessation of the pain, while in the remaining twenty-three this information was lacking. In other cases not included in this series, careful questioning has led us to conclude that the pain most often gradually increases in severity, reaches a plateau and then gradually declines.

Severity.—In only three cases (cases 16, 25 and 29) was pain relatively minor. In the other twenty-six cases it was severe, sometimes requiring repeated hypodermic injections of morphine, as in case 22. It must be remembered that the intensity of pain may change during the various stages of the disease. This fact is emphasized by the following groups of cases: In one group (cases 16, 25 and 29), pain was relatively mild. In another (cases 4, 9, 13, 17, 18, 23 and 27), the attacks, which were relatively mild early in the disease, became severe later on. In still another group, illustrated by case 14, the attacks were mild at first, then severe and finally mild again in the later years of the disease. A fourth group comprises those cases in which there have been severe attacks throughout the known history of the disease to date. In addition, there were minor or abortive attacks scattered among the severe ones. This group consists of cases 1, 3, 5, 6, 7, 8, 10, 15, 19, 20, 21, 24 and 26. In a fifth group (cases 2, 11, 12, 22 and 28), are those who had severe pain early, followed by a milder pain later in the disease. The patient in case 22 received only slight relief of pain from opiates.

Frequency.—The painful seizures may be few or many. Just as the intensity of pain changes, so does the frequency of attacks in some cases. Thus, in one group (cases 2, 4, 6, 9, 11, 16, 18, 19, 23, 26 and 27), there was a progressive increase in frequency of attacks. In cases 6, 11, 16, 19, 26 and 27 the frequency of attacks progressed to almost daily pain. In cases 20, 25 and 28, the attacks decreased in frequency. In another group of thirteen cases the patients did not experience any material change in the frequency of attacks. Frequency was unspecified in four cases. The extremes are illustrated by case 10, in which the attacks were as infrequent as every six years, and case 17, in which the attacks came as often as four or five times daily.

Location.—The primary or first site of pain was in the epigastrium in fourteen cases (cases 1, 2, 4, 5, 8, 10, 11, 14, 16, 17, 21, 24, 26 and 28), in the right upper quadrant of the abdomen in eight cases (cases 3, 9, 12, 13, 19, 20, 25 and 27), in the left upper quadrant in three cases (cases 18, 22, and 23), in the right lower quadrant in one case (case 7), generalized over the abdomen in two cases (cases 6 and 29) and in the periumbilical region in one case (case 15).

Character of pain.—Pain was described by several different adjectives, sometimes by two or more in the same case. Pain was cramping in five cases, stabbing in three, burning in two, gnawing in one, steady in nine, sharp in four, dull in one and unspecified in ten cases. However, careful questioning of patients not included in this series has led us to conclude that the pain of pancreatitis is prone to be steady rather than colicky or undulatory, as in biliary colic.

Extension of pain.—The direction and site of extension of pain may give a valuable clue in the diagnosis of pancreatitis, particularly when pain spreads to the left. However, pain may be confined to the right upper quadrant of the abdomen and thus make one suspect biliary colic. In fifteen cases it was stated that pain extended to the lower thoracic and upper lumbar regions, in six cases to the left upper quadrant of the abdomen, in three cases to the right upper quadrant, in one case (case 23) to the left lower quadrant, in five cases to the entire abdomen, in one case (case 10) to the left anterior region of the thorax, in four cases to the right scapular region and in two cases to the left shoulder. In two cases there was no shift of pain and in two cases information was unavailable. When pain is felt in the left portion of the back, it may be localized to the left costovertebral angle.

It has been stated (5) that, in a general way, disease confined chiefly to the unciform process causes pain to extend to the right iliac fossa or right renal region; disease in the head of the pancreas causes pain to extend to the right hypochondrium and the region of the right shoulder, and disease involving the body and tail of the pancreas causes pain to extend to the left hypochondrium, left anterior region of the thorax, left shoulder and left lumbodorsal region. We have attempted to study our cases with this idea in mind and we gain the im-

pression that this statement is roughly, but not strictly, true. When pain was located across the entire epigastrium and lumbodorsal region of the back or when it was generalized over the abdomen, the entire pancreas was usually involved. In five of eight cases in which pain started in the right upper quadrant of the abdomen, the lesion was confined chiefly to the head of the pancreas: In nine of twelve cases in which the initial pain was epigastric, the process was diffuse throughout the pancreas. Case 10 is interesting in that the pathologic lesion, as noted at the time of operation, was confined to the midportion of the pancreas. In this case pain was in the epigastrium and extended to the left anterior region of the thorax. It is when the pain is confined to the right upper quadrant of the abdomen and right posterior region of the thorax that one is likely to be misled into thinking of cholecystic disease. However, the steady and prolonged nature of pain and its gradual progression and decline should raise the question of pancreatic origin.

TABLE 1
Duration of seizures of pain in cases of chronic pancreatitis (27 cases)

DURATION OF PAIN	CASES
Less than 1 hour.....	1
1 to 5 hours.....	2
6 to 11 hours.....	1
12 to 23 hours.....	1
2 to 6 days.....	6
7 to 13 days.....	7
14 to 20 days.....	1
21 to 27 days.....	2
28 to 35 days.....	6

Factors which affect the intensity of pain.—The painful seizures are usually not relieved by anything but opiates. However, in cases 9 and 23 enemas

afforded some relief, in case 28 bending forward was beneficial, in case 2 emesis was helpful and in cases 4, 9 and 18 less pain was experienced when the patients kept quiet than when they were active. Eating seemed to aggravate the pain in four cases, exercise in two cases and respiration in two cases.

Duration of seizures.—The duration of painful seizures is often a helpful differential point between pancreatitis and disease in the biliary tract. The pain of pancreatitis is likely to last for days, as noted in table 1. Specific examples are case 5, in which the attacks often lasted two weeks, and case 21, in which the seizures lasted two to nineteen days.

Associated symptoms.—The painful seizures may be accompanied by nausea, emesis, constipation, diarrhea, fever, chills or jaundice. Fever may last for

days. In fourteen cases there was a history of fever with the attacks. In cases 13 and 26 the attacks seemed to begin with diarrhea. In cases 4, 14, 15, 16, 25, 26, 28 and 29 there was a history of diarrhea accompanying the pain. Temporary ileus is suggested by certain patients who feel that all intestinal activity tends to cease during an attack and then, as the pain begins to subside, loudborborygmi and the passage of flatus begin to occur. A history of jaundice was given in eight cases, of hematemesis or melena in two (cases 8 and 23), of cyanosis and "shock" in three, of emesis in twenty and of chills in four cases. We believe these data are understatement, since information was incomplete in some histories.

Symptoms in intervals between seizures of pain.—In five cases there was no dyspepsia between the attacks of pain. A postprandial feeling of abdominal fullness, particularly after fatty foods had been eaten, was noted in ten cases, mild pains in the upper part of the abdomen in five, constipation in two, diarrhea in two, anorexia in three, tenderness in eight, recurring hematemesis in one (case 8) and recurring hematemesis and melena in one (case 23).

The physical findings. During seizures.—Only a small number of patients were actually seen during one of the attacks of pain. Many were seen shortly after an attack. In most of the cases there was evidence of loss of weight. Complete data in this respect were available in twenty-two cases. The average weight of the patients on admission to the clinic was 134 pounds (60.8 kg.). They had lost an average of 25 pounds (11.3 kg.) or 15.7 per cent of their former weight.

The temperature may be moderately high, as in case 13, in which it was 101.5°F. In general, patients had essentially normal temperatures when they were seen at the clinic. In four cases (cases 11, 15, 16 and 21), there was slight elevation of temperature. In case 15 the patient had a subnormal temperature when admitted to the hospital with acute hemorrhagic pancreatitis. He was in shock. However, within a few hours, a high fever developed because of what later proved to be peritonitis and hepatic abscesses. A rather high, sustained fever makes one suspect pancreatic necrosis or some other complication such as abscess, peritonitis or pylephlebitis.

There is nothing characteristic about the pulse rate in these cases. As during most acute, painful states, there is a tendency toward tachycardia.

Jaundice was present on admission in ten of eighteen cases studied. In seven of these it was latent, being detected only by the serum bilirubin test. In three cases it was clinically manifest. The concentration of bilirubin was low, generally from 1 to 3 or 4 mg. per 100 c.c. of serum and the van den Bergh reaction was always direct. The highest concentration of bilirubin was 6.8 mg. per 100 c.c. of serum (case 4).

Shock was apparent in cases 10 and 15, being mild in the latter case.

In case 15 the skin over the thorax and arms had a peculiar bluish mottling when the patient was admitted to the clinic. In case 9 cyanosis was observed during a painful seizure.

Tenderness and muscular spasm, elicited in thirteen cases, were usually confined to the epigastrium, more often on the left than on the right. In some instances there was tenderness in the left costovertebral angle. Definite rigidity of the abdomen was not mentioned in the records.

In cases 6, 11, 14, 19 and 25, an epigastric mass was noted and surgical exploration in four of these cases revealed a pancreatic cyst.

The spleen was palpably enlarged in cases 4, 11 and 28.

The liver was enlarged in cases 3, 4, 14, 15, 16, 21 and 28.

Ascites was present at one time in cases 16 and 28.

Between seizures.—Jaundice was noted three weeks after an acute attack of pancreatitis in case 10 and was chronic in case 4. In the latter case the chronicity of the jaundice was due to chronic hepatitis.

Epigastric tenderness was a common finding between the acute seizures.

A pancreatic cyst was palpable between the attacks in cases 6, 19 and 23. An indeterminate mass was noted in the left portion of the epigastrium in case 11; this may have been a pancreatic cyst.

Splenomegaly was noted in two cases (cases 11 and 28) and hepatomegaly in six cases (cases 3, 4, 14, 16, 21 and 28) between the painful seizures.

Ascites and peripheral edema were observed in cases 16 and 28. In case 16 there was severe hypoproteinemia.

Laboratory data. Urinalysis.—The urine may exhibit albuminuria of varying degree during or even after a severe seizure. In this series, albuminuria, grade 1, was noted in three cases, grade 2 in eight cases and grade 3 in one case. Glycosuria, grade 1, was noted in seven of the twenty-nine cases, grade 2 in one case and grade 3 in two cases. Thus, in 34 per cent of all the cases there was glycosuria. In some instances this was only transient, occurring during one of the acute exacerbations of pain. In others it was due to frank diabetes. In three cases, in which the patients were male, erythrocytes, grade 1, were found in the urine. Pyuria of significant degree was not observed. Tube casts were noted in one case.

Studies of the blood.—Slight anemia, mostly hypochromic, was observed in some cases, especially those in which there was rather chronic advanced pancreatic disease. Thus, six males and three females had a concentration of hemoglobin of less than 12 gm. per 100 c.c. of blood. The erythrocyte count was largely normal. Three males and three females had counts of less than 4,000,000 per cubic millimeter of blood.

Leukocytosis was not an important finding, since in twenty-one of the twenty-nine cases leukocytes numbered 10,000 or less per cubic millimeter of blood.

Five of the twenty-one normal counts were made during acute seizures of pain. Leukocytosis was present in the remaining eight cases. In four of these cases leukocytes numbered between 10,000 and 15,000 in each cubic millimeter of blood. In one (case 4) leukocytes numbered 15,600 and in three leukocytes numbered more than 20,000 in each cubic millimeter of blood. In six of the eight cases the leukocytosis was found during an acute attack of pain. Hemorrhagic pancreatitis was present in one case; subacute pancreatitis with fat necrosis was noted in case 4, and pancreatic cyst (inflammatory) was noted in one of the six cases. In the other two cases, the leukocytosis was observed in the interval between attacks but could be explained by intercurrent infection. In short, leukocytosis was present in about 50 per cent of the cases in which the patient was examined during an acute attack but the leukocytosis was not indicative of any specific pathologic process.

In case 6 there was eosinophilia of 8 per cent and in case 17 eosinophilia of 6 per cent.

Macrocytosis was noted in cases 4 and 21 and was apparently due to hepatitis. A "toxic" hematologic appearance was observed in cases 10, 15 and 21.

Blood chemistry.—The concentration of urea in the blood may be elevated during the severe seizures (as in cases 2, 13, 15 and 29).

The fasting concentration of blood sugar was determined in twenty-three cases. It was more than 120 mg. per 100 c.c. of blood in six cases (cases 15, 16, 21, 27, 28 and 29). The elevation was transitory (during acute seizures only) in two cases (cases 15 and 21) and permanent in four (cases 16, 27, 28 and 29). Diabetes was also present in case 23 and developed after the patient had left the clinic in cases 22 and 24. Thus, diabetes was present in seven (24.1 per cent) of the twenty-nine cases of this series.

The glucose tolerance test was performed in eight cases, in six of which the result was positive (cases 4, 6, 11, 12, 14 and 24). The result of the test, which was positive in case 4 before operation, became negative when attacks of pain ceased and improvement ensued after surgical drainage of the gallbladder. Case 24 is interesting in that the patient had a normal fasting blood sugar and a positive glucose tolerance test in 1940, nineteen years after the onset of the painful attacks. At the time of latest information she had diabetes mellitus, twenty-four years after the onset of the attacks of pain and five years after the glucose tolerance test was found to give a positive result. While a low carbohydrate intake may frequently characterize the diet of patients ill with, and malnourished from, chronic pancreatitis and may influence the results of the test, the glucose tolerance test may be used with due precautions in detecting diminution of reserve of islet cell function due to the disease.

In all but one case the concentration of cholesterol, cholesterol esters, lecithin, fatty acids and total lipoids in the plasma fell within the extremes of values

found in normal persons of the same age groups. The values, observed between painful seizures, were low in case 25. In this case, the hypolipemia is adequately explained by the emaciation, malnutrition and steatorrhea.

The concentration of bilirubin in the serum was determined in twenty-one of the twenty-nine cases. It was normal in ten, and elevated in eleven cases, in which the values varied from 1 to 3 mg. per 100 c.c. of serum, except for case 4 in which the value was 6.8 mg. per 100 c.c. The van den Bergh reaction was direct in those cases in which values were elevated. In five of the eleven cases in which there was hyperbilirubinemia, it was noted during painful seizures (cases 1, 2, 11, 13 and 16), and in six it was noted between the seizures (cases 4, 10, 14, 21, 25 and 28). Involvement of the head of the pancreas with obstruction of the common bile duct appears to be the chief but not the sole pathologic basis for hyperbilirubinemia. Damage to the liver also may be responsible, as it seemed to be in cases 4, 10, 16 and 28.

The sulfobromophthalein test of hepatic function was done in fifteen of the cases. Retention of dye, grade 1 to 3, was noted in seven cases (cases 6, 10, 11, 15, 21, 25 and 28), but in all of them except case 6 latent jaundice was present. The test gave positive results during a painful seizure in cases 6, 11, 15, 16 and 25. In two of the seven cases a second test, performed after the effect of the acute exacerbation of the disease had passed, did not disclose retention of dye.

Values for activity of amylase in the serum were determined in twenty-two, and those for lipase in the serum in eighteen of the twenty-nine cases. In eight cases these values were noted during painful attacks. In two of the eight cases (cases 4 and 6), the values for both enzymes were elevated. In two cases (cases 11 and 23) the value for amylase was elevated, but that for lipase was normal, while in two cases (cases 24 and 26) the value for lipase was high and that for amylase was normal. In short, in six of the eight cases, values for amylase or lipase or both were elevated.

The serum amylase or lipase or both were elevated in three cases (cases 12, 19 and 21) between the painful seizures. Serum amylase was high in all three cases. In case 21 it was above normal four days after the attack had ceased. Serum lipase was above normal in cases 12 and 21, being elevated in case 21 four days after cessation of the attack of pain.

The sedimentation rate of the blood was tested in fourteen cases, in ten of which it was increased. The rate was normal (less than 20 mm. in one hour, Westergren method) in four cases (cases 3, 12, 19 and 23), between 20 and 40 in cases 4 and 22, between 40 and 60 in three cases (cases 7, 13 and 20) and more than 60 in five cases (cases 1, 2, 11, 15 and 23). A rapid rate was noted during the painful seizures in seven (cases 1, 2, 4, 7, 11, 13 and 15) and between painful seizures in three (cases 20, 22 and 25). In case 25 the elevated rate seemed to be due largely to subhepatic infection resulting from leakage at the site of cholecystogastrostomy.

The concentration of calcium in the serum was determined in six cases, in one (case 11) during an attack of pain and in five between the attacks. The concentration was abnormally low in one case (case 16), the hypocalcemia being part of a generalized deficiency state. Values in the other five cases (cases 4, 11, 27, 28 and 29) were normal.

The prothrombin time (Quick method) was determined in eleven cases, in eight of which it was increased and in three of which it was normal (18 seconds). In six (cases 2, 4, 10, 15, 16 and 25) it ranged between 20 and 30 seconds and in two (cases 16 and 26) between 30 and 40 seconds. In each of these eight cases there were jaundice and hepatic damage sufficient to explain the abnormality. Values in cases 2, 4, 15, 16 and 25 were observed between the attacks.

The concentration of proteins in the serum was determined in seven cases (cases 4, 11, 16, 23, 25, 28 and 29), the values in all of these being obtained between the attacks. Hypoproteinemia (less than 6.0 gm. per 100 c.c. of serum) was observed in two cases (cases 16 and 29). In case 16 the serum proteins varied from 2.8 to 5.6 gm. per 100 c.c. and the hypoproteinemia was part of a generalized deficiency state. In case 29 a minimum of 5.4 gm. per 100 c.c. of serum was observed but the albumin-globulin ratio was normal.

Examination of stools.—Stools were tested in seven cases for excess of fat because of a clinical picture of steatorrhea. The percentages of fat to dry weight were respectively 14.5, 11.2, 62.7, 50.9, 50.3, 67.3 and 22.5 in cases 3, 4, 16, 25, 26, 27 and 29. In four additional cases (cases 12, 14, 23 and 24) microscopic examination of the stool for excess of fat revealed such an excess only in case 24. Clinically, fourteen patients had steatorrhea, which was controlled by a diet low in fat and by the administration of pancreatin. In all the cases except 16 and 27 studies were done between the attacks of pain.

Secretin test.—This test was performed in eight cases, in all of which there was decreased response to stimulation of pancreatic function by the use of secretin. This response was reflected in lowered values for amylase, lipase, volume or pH when compared with normal standards (Comfort and Osterberg) (6).

Analysis of gastric contents.—There was nothing characteristic about the gastric acids in the eighteen cases in which tests were made. Free hydrochloric acid was less than 20 units in two cases, between 20 and 40 units in ten cases and more than 40 units in three cases. In three cases there was achlorhydria. In cases 4 and 27 the more important finding of retention of gastric contents was noted.

Gastroscopy.—Gastroscopic examination, made in one case (case 23), revealed deformity of the stomach from extragastric pressure. In cases not of this series gastritis has been found.

Röntgenologic examinations. Gallbladder.—Cholecystograms were made in twenty-two cases, of which twenty cases were satisfactory for diagnosis. In

sixteen of these there was normal function; in four (cases 2, 3, 7 and 25) there was no evidence of function. In one of the four cases (case 7) a reason for failure of the gallbladder to concentrate the dye was not found on surgical exploration. The gallbladder appeared normal. The same was true for case 3 but here the gallbladder was infected with *Giardia lamblia*. In case 2 the common bile duct and gallbladder were dilated and jaundice was present. These changes were secondary to obstruction of the common bile duct and adequately explained the failure of the gallbladder to function. In case 25 the common bile duct was dilated and the gallbladder was enlarged and edematous but jaundice was absent and hepatic function was excellent. These changes may or may not explain the lack of function of the gallbladder. Roentgenologic evidence of a nonfunctioning gallbladder may lead to confusion in diagnosis in cases of pancreatitis.

Pancreas.—Roentgenologic examinations disclosed calcification of the pancreas in fourteen of the twenty-nine cases. Special roentgenograms of the pancreatic region were made in eight cases, in five of which the roentgenograms gave evidence of calcification. In the remainder of the fourteen cases pancreatic calcification was revealed by means of cholecystograms, simple roentgenograms of the abdominal region or roentgenograms of the region of the kidneys, ureters and bladder.

Stomach.—Roentgenographic examination of the stomach and duodenum in these cases was of considerable interest. In case 1 antral gastritis was noted on roentgenoscopic examination but this was not confirmed at operation a few days later. However, there was pancreatitis, which involved the head and body of the pancreas. In case 14 there was rapid gastric emptying. In case 18 there were apparent obstruction, dilatation and retention. At operation the stomach was found to be adherent to the pancreas. In case 4 obstruction and dilatation of the stomach were not suspected but barium was retained in the stomach for twenty-four hours. Marked dilatation of the stomach in case 27 was confirmed at operation but a satisfactory cause for such findings was not revealed. In cases not reported in this series definite obstruction of the duodenum by the enlarged head of the pancreas has been noted. In case 15 the duodenum was deformed by an extrinsic mass. Roentgenologic finding of deformity of the lower third of the stomach in case 23 was due to a pancreatic cyst. In cases 9, 18 and 22 the roentgenologic deformity of a duodenal ulcer was unassociated with ulcer dyspepsia. In case 18 the roentgenologic examination suggested duodenal obstruction with some gastric dilatation and retention but at operation the surgeon could not find an ulcer. In case 9 the deformity was found at the time of operation to be due to adhesions between the duodenum and the gallbladder; when the adhesions were severed the deformity vanished. In case 22 operation was not performed. It is well to re-

member that pancreatitis may impair the motility of the stomach and duodenum and even physically obstruct the duodenum.

Small bowel.—Roentgenographic examination of the small bowel revealed a pattern suggestive of a deficiency state in case 16 although motility seemed normal. In case 4 marked hypomotility and apparent edema of the small intestine were observed. The condition was suggestive of chronic idiopathic steatorrhea.

Colon.—Nothing significant was noted on roentgenographic study of the colon except that the examiner occasionally noted that shadows characteristic of calcification overlay the pancreatic region. In case 16 the picture was vaguely suggestive of ulcerative colitis.

Region of kidneys, ureters and bladder.—Roentgenograms of the region of the kidneys, ureters and bladder were taken in many cases to help exclude the kidneys as a cause of pain. Pancreatic calcification was frequently observed in such roentgenograms. In case 6 a simple roentgenogram of the abdomen revealed an epigastric mass which surgical exploration proved to be a pancreatic cyst.

Preoperative diagnosis.—The difficulty that physicians have in making a preoperative diagnosis of pancreatitis is reflected in the following diagnoses made in twelve cases in which operation had not been performed prior to the patient's admission to the clinic: "appendicitis" in two cases, "amebiasis" in one, "heart attack" in one, "indigestion" in two, "intestinal influenza" in one, "peptic ulcer" in two, "intestinal obstruction" in one and "cholecystic disease" in two. The difficulty of making a diagnosis of pancreatitis was also encountered by the surgeon at operation. In eleven cases there had been previous operations, sometimes multiple, for the recurring seizures of pain. Intestinal obstruction, cholecystic disease and peptic ulcer were the more frequent diagnoses. In two instances an operative diagnosis of appendicitis was made and appendectomy was performed but the attacks continued to occur.

The same difficulty in arriving at a correct diagnosis preoperatively was encountered at the clinic. Preoperative diagnosis at the clinic was correct in 41 per cent, partially correct (pancreatitis given among other possible diagnoses) in 23 per cent and incorrect in 36 per cent of the twenty-two cases in which operation was performed. The most common erroneous diagnoses were cholecystic disease in eight cases and duodenal ulcer (penetrating, acutely perforating or obstructing) in four cases.

Surgical findings. **Pancreas.**—In some instances the surgeon described the pancreas as hard or firm, at other times as hard and nodular like a carcinoma (cases 2, 4 and 16), and again as having diffuse, inflammatory edema. In cases 5, 7, 8, 12, 25 and 28 the process was diffuse. In cases 17, 25 and 27 there was calcareous pancreatitis which was diffuse from head to tail in case 27.

A localized swelling in the head of the pancreas at the location of some large pancreatic calculi was noted in case 17. In one instance (case 15) there were extensive hemorrhage, edema and necrosis of the pancreas. The pathologic process in case 10 seemed confined chiefly to the midportion of the pancreas.

In case 19, at the first operation, a "necrotic pancreatic cyst, 5 cm. in length," was found, and at the second operation a "unilocular cyst about 10 to 11 cm. in diameter," the walls of which contained "sandy calcific particles," was found. In case 23 the cyst was much larger than in case 19 (18 to 20 cm. in length) and was multilocular. It seemed to be either "an old hematoma or pancreatic cyst." In case 6 the cysts were multiple; one was small and the other very large, containing 2,800 c.c. of dark fluid in which pancreatic enzymes were present. The walls of the cyst were composed of fibrous inflammatory tissue, the lining of the cyst consisting of fibroblasts. In case 14 the cyst was also large and contained dark red fluid. The description of the cyst and its contents in each case suggested that the cyst was the result of hemorrhagic necrosis of the pancreas.

The surgeon observed definite pancreatic necrosis in two cases (cases 13 and 15), an abscess being found in the latter case. Intraperitoneal abscess was found in case 23. Peripancreatic inflammation was observed commonly, as illustrated in case 18, in which the tail of the pancreas was adherent to the fundus of the stomach. Peripancreatic necrosis was noted in four cases (cases 1, 6, 18 and 19).

Common bile duct.—Dilatation of the common bile duct was observed frequently. The duct was described as dilated only in cases 2, 9, 13, 14 and 25, as dilated and thickened in case 28 and as dilated but thin-walled in case 27. It was described as twice normal size in cases 14, 25 and 28 and three times normal size in case 2. The common bile duct was not dilated in six cases (cases 1, 3, 7, 10, 12 and 18). In case 10 there was apparently congenital absence of the gallbladder and yet the common duct seemed to be normal on inspection and palpation. Pancreatitis in this case seemed to be chiefly in the body of the pancreas.

Gallbladder.—In cases 5, 13 and 14 the gallbladder was mildly diseased and its walls were thickened. In case 13 the gallbladder was described as edematous and thick-walled and in case 25 as normal in size, edematous but not containing stones. The gallbladder was dilated and thin walled in six cases (cases 2, 4, 15, 25, 26 and 27). It was several times normal size in case 2 and greatly enlarged in case 26.

The pathologic state of the gallbladder is of especial interest in this study because the cases have been chosen on the basis of absence of a degree of primary cholecystic disease sufficient in our opinion to influence the clinical picture. That this is true in cases 5, 10 and 14 will be accepted without question,

for it is inconceivable that the degree of cholecystic disease present in these cases could have caused symptoms as severe as those presented by these patients. That this is true in cases 2, 4, 15, 26, 27 and 28 will in all probability be accepted when one recalls that dilatation of the gallbladder alone is evidence, not of primary disease of the organ, but of increased pressure in the extrahepatic biliary tract (obstruction of the cystic duct excluded).

That the gallbladder is not sufficiently diseased to influence the clinical picture in cases 13 and 25 may not be accepted without protest. In case 13 it should be noted that demonstration of excellent function before and after operation and the presence of only very mild disease in the gallbladder at necropsy are evidence that the edema of the gallbladder was transitory, possibly secondary to acute episodes of pancreatitis. In case 25 the degree of edema was not stated but it must have been slight, since the surgeon could utilize the gallbladder to effect cholecystogastrostomy. Furthermore, the associated dilatation of the common bile duct and the history of alcoholic stools, dark urine and jaundice in one or more attacks of pain, which was far too severe for explanation by the degree of cholecystitis present, suggest that the process in the gallbladder was secondary to the pancreatitis. All in all, we believe that primary cholecystic disease was absent or minor in the cases of this series. Thus it is well to note that pathologic changes in the gallbladder may be secondary to the pancreatitis, with the result that the gallbladder may be utilized in the more conservative operative procedures such as cholecystogastrostomy or cholecystoduodenostomy in the treatment of chronic pancreatitis.

A dilated gallbladder is rarely felt in cases of primary pancreatitis. This is understandable in view of the slight degree of dilatation of the gallbladder as described in most cases at operation. However, in cases 2 and 26 the degree of dilatation was probably sufficient to permit palpation on careful examination. In case 2 there was sufficient spasm of the rectus muscle to prevent palpation of the organ. In case 26, as far as is known, conditions were such that the gallbladder might have been felt. It is well to recognize that in rare instances the gallbladder, in cases of obstruction of the common bile duct due to chronic pancreatitis, may be felt as in malignant obstruction of the duct.

Liver.—In cases 4 and 10, hepatitis was found. In each case jaundice was present but the common bile duct was normal in size. In the absence of obstruction of the common bile duct, it is necessary to consider the possibility that the process called pancreatitis, be it inflammatory or otherwise, likewise involved the liver. It is more probable that both the jaundice and the hepatitis were secondary to an unrecognized obstruction of the common bile duct.

In two cases (16 and 28) the liver was found normal in appearance at operation or necropsy but in each case the clinical evidence left no doubt that transi-

tory disturbances of hepatic function, with hepatomegaly, jaundice and ascites, occurred. The nature of the disturbance is not clear. It may have been a fatty liver associated with deficiency of lipocaic as suggested by Snell and one of us (Comfort) in case 28 (7) but it may also have been due to alcoholism and dietary deficiency.

Spleen.—This organ was enlarged to three or four times normal size in case 4, in which there were also considerable hepatitis and perihepatitis.

Stomach.—Inflammation about the pylorus was noted in case 15. The stomach was adherent to the pancreas in case 18. The pylorus was thickened in cases 8 and 18.

Duodenum.—Adhesions between the gallbladder and the duodenum explained the roentgenologic deformity characteristic of duodenal ulcer in case 9. When the adhesions were out the deformity vanished. In cases not included in this series, there was actual obstruction of the duodenum by the enlarged pancreas.

Jejunum.—In case 6 the first part of the jejunum was partially obstructed by pressure of a large pancreatic cyst.

Veins.—In case 18 large dilated veins were noted in the mesentery of the transverse colon and in the greater omentum. In case 13 the gallbladder was covered by large vessels. In case 27 there were many large varicosities in the upper part of the abdomen and there appeared to be obstruction of the superior mesenteric veins.

Pathologic anatomy.—The following description of the lesions occurring in the pancreas in cases of chronic relapsing pancreatitis is based on the observations at necropsy in three cases and on observations and biopsies obtained during the course of surgical procedures in seven cases.

Gross appearance.—The pancreas was described as indurated in seven cases and as nodular in two cases. Atrophy was noted in two cases, while in one case the pancreas was larger than normal. Infiltration with fat was extensive in one case. Pseudocysts were found in four cases. These varied in size from 1.0 cm. to 20.0 cm. in greatest diameter. The contents of these pseudocysts varied from cloudy, colorless fluid to yellowish green, semisolid necrotic material. The latter was interpreted as the result of the digestive action of pancreatic enzymes on necrotic pancreatic tissue and blood. Chemical analysis of the contents of these cysts was carried out in four cases and varying amounts of pancreatic enzymes were found. Macroscopic calcification in the pancreas was described in three cases and so-called fat necrosis in the adipose connective tissue adjacent to the pancreas was found in two cases. The common bile duct revealed varying degrees of dilatation in five cases, while the gallbladder was dilated in four cases. In one case in which the common bile duct was dilated, the gallbladder had been previously removed. Chronic cholecystitis was present in two cases.

Histologic examination.—Fibroblastic proliferation and fibrosis were prominent features of all sections of the pancreas examined. Interlobular fibrosis was more pronounced than intralobular or interacinar fibrosis. Interlobular fibrosis was mild in two cases and moderate in four cases. Intralobular fibrosis was mild in four cases and moderate in two cases. In four cases, the biopsy did not reveal a lobular arrangement but only masses of fibrous connective tissue. The acini were atrophied and disorganized. Frequently they appeared as small groups of cells without the normal arrangement around a central lumen. The islands of Langerhans also were frequently atrophied. Separation of the islet cells as if by edema was a frequent occurrence. Sometimes the cells were arranged in ribbons, which were widely separated.

Lymphocytes and plasma cells were present in moderate numbers in all cases. They were found diffusely distributed throughout the regions of fibrosis and also in focal collections. In four cases a perineural distribution of lymphocytes was prominent. Eosinophilic leukocytes were present in the interstitial connective tissue in moderate numbers in three cases. Actual suppuration was observed in only one case. This occurred in the wall of a resolving abscess, which had perforated and drained spontaneously into the duodenum. Foreign body giant cells were present in three cases. They were usually found in association with cholesterol crystal clefts. Deposits of hemosiderin were observed in five cases while deposits of calcium in the interstitial connective tissue were observed in three cases.

There was histologic evidence of slight to moderate dilatation of the ducts in four cases. Laminated material, probably inspissated mucus, was present in two cases. So-called squamous metaplasia or squamatization of the epithelium of the ducts occurred in one case.

Arteriosclerosis was pronounced in some cases. The most prominent change was a proliferation of connective tissue cells which had led to thickening of the intima and narrowing of the lumen. Arteriosclerosis was absent or of mild degree in three cases, moderate in two and severe in four cases.

Surgical procedures and results.—Surgical operations were carried out in twenty-two of the twenty-nine cases reviewed. The results in eighteen cases in which adequate postoperative follow-up data are available are shown in table 2.

Internal or external drainage of the biliary tract, carried out alone or with some other surgical procedure in seventeen of the eighteen cases, was followed by complete remission of acute exacerbations in seven cases and by considerable relief in four cases. This improvement cannot be ascribed with certainty in every case to the surgical procedure carried out nor can the improvement be associated with the degree of pancreatitis or the duration of drainage. It is interesting to note that both pancreatolithotomy and drainage of a cyst have likewise been followed by remission of acute exacerbations.

TABLE 2

Data on cases of chronic pancreatitis in which operation was performed and in which adequate postoperative follow-up data are available

RESULT	CASE	DIAGNOSIS	OPERATION	AVERAGE FREQUENCY OF ATTACKS		POST-OPERATIVE FOLLOW-UP INTERVAL
				Preoperative	Postoperative	
Complete relief (39 per cent)	1	Subsiding acute pancreatitis	Cholecystostomy and drainage of gallbladder for 2 wks.	1 attack 2 days pre-operatively	None	2½ yrs.
	2	Chronic pancreatitis	Cholecystogastrostomy	12 yearly	None	1½ yrs.
	4	Chronic pancreatitis, hepatosplenomegaly	Cholecystostomy and drainage of gallbladder for 1 mo.	12 yearly	None	8 mos.
	10	Chronic pancreatitis	Choledochostomy and T tube drainage for 2 yrs.	4 yearly	None	3½ yrs.
	17	Chronic pancreatitis, calculi in ducts of Wirsung and Santorini	Partial pancreatolithotomy followed by roentgen treatment	12 or more a yr.	None	2 yrs., 1 mo.
Considerable relief (22 per cent)	23	Chronic pancreatitis, pancreatic cyst, pancreatic calcification, diabetes mellitus, intraperitoneal abscess	Drainage and marsupialization of pancreatic cyst, drainage of intraperitoneal abscess	2 or more a yr.	None	2½ yrs.
	28	Chronic diffuse pancreatitis, pancreatic calcification, pancreatic steatorrhea, diabetes mellitus	Choledochostomy and T tube drainage for 4 mos., cholecystostomy with drainage	1.4 yearly	None	9 yrs.
	12	Chronic pancreatitis	Choledochostomy with T tube drainage for 18 days, cholecystostomy with drainage	4 yearly	3 severe ones since operation, few minor ones	4 yrs., 2 mos.
	19	Chronic pancreatitis, pancreatic calcification, pancreatic cyst	Pancreaticocystoduodenostomy	3 yearly	Less frequent, shorter, milder	1 yr., 1 mo.
	25	Chronic pancreatitis, pancreatic calcification, pancreatic steatorrhea	Choledochostomy, cholecystogastrostomy, partial removal pancreatic calculi	12 to 24 attacks yearly	No severe ones, several minor ones	2 yrs., 8 mos.
Slight or no relief (39 per cent)	26	Chronic pancreatitis, pancreatic calcification, pancreatic steatorrhea	Partial pancreatolithotomy, cholecystojejunostomy	"Many" yearly	2 minor ones in 2 yrs.	4 yrs.
	3	Chronic pancreatitis	Cholecystostomy	12 yearly	4 in first yr.	1 yr.
	6	Chronic pancreatitis, pancreatic cyst	Drainage and marsupialization of cyst	6 yearly	6 in 10 mos. no data for 3 yrs.	10 mos.
	8	Chronic pancreatitis, pancreatic calcification	Partial gastrectomy (posterior Polya anastomosis), partial duodenectomy	2 yearly	6 yearly	3 yrs.
	9	Chronic pancreatitis	Choledochostomy with T tube drainage for 6 mos., cholecystostomy with drainage	6 yearly	No change	3 yrs.
	13	Chronic pancreatitis	Cholecystostomy, choledochostomy with T tube drainage for 1½ mos.	8 in 7 yrs.	7 in 4 yrs., 9 mos.	4 yrs., 9 mos.
	14	Chronic pancreatitis, pancreatic cyst, pancreatic steatorrhea	Drainage and marsupialization of cyst, choledochostomy and T tube drainage for 3 wks., cholecystectomy	3 or more a yr.	Not severe in past 3 yrs.	8 yrs.
Slight or no relief (39 per cent)	27	Chronic pancreatitis, pancreatic calcification, pancreatic steatorrhea, diabetes mellitus	Cholecystogastrostomy	6 to 12 a yr.	None for 1 yr., then 6 to 12 a yr. or more	1 yr., 7 mos.

GENERAL COMMENT

From the preceding analysis of data on twenty-nine cases of chronic relapsing pancreatitis, a description of pancreatitis unassociated with other disease in the upper part of the abdomen of a degree sufficient to alter or color the picture may be drawn.

The analysis emphasizes several points. First, chronic pancreatitis characteristically is a disease of recurring, acute exacerbations, separated by short or long periods of relative clinical quiescence. Second, during the early stages of the disease, during the periods of quiescence, the clinician may not be able to demonstrate, by physical or laboratory methods of examination, existence of the pathologic physiologic changes which are characteristic; yet the surgeon or pathologist will be able to demonstrate pathologic changes in the organ. The cases of group 1, especially case 13, in which necropsy studies were possible, demonstrate the chronicity of the process in the pancreas in the absence of demonstrable physiologic changes. Clinically, it is in such cases that an accurate description of the painful episodes is important to the clinician in making a presumptive diagnosis of pancreatitis. In such cases in which there are long asymptomatic intervals and negative examinations the clinician may well prefer the term "recurring acute pancreatitis." Sooner or later, however, the destruction of the pancreas usually will reach the point where disturbances of internal and external secretion, pancreatic calcification and other sequelae will be demonstrable at all times. Acute painful exacerbations separated by periods of relative clinical quiescence were present at some time in twenty-eight of the twenty-nine cases studied. In some of these, the duration of the painful seizures became so prolonged and that of the pain-free interval so short that the pain appeared to be chronic. In one case the disease appeared to have been essentially painless, its first manifestation being diabetes, followed in three years by steatorrhea. Third, the clinical picture is due not only to the disease in the pancreas, but also to the effect of the disease on the neighboring organs, including the stomach, duodenum, small bowel, liver, biliary tract and blood vessels. Fourth, pathologic changes are mild to severe, varying from edema to necrosis or to chronic destruction of the pancreatic parenchyma with resulting fibrosis.

Description of chronic relapsing pancreatitis falls naturally into the following divisions: (1) pathology; (2) the incidence, onset and precipitating factors; (3) the acute, painful exacerbations; (4) the sequelae arising from the effects of the disease on the pancreas; (5) the sequelae arising from pressure of the enlarged pancreas on neighboring organs; (6) the sequelae arising from involvement of the neighboring organs by the disease; (7) other sequelae; (8) the termination of the disease; (9) diagnosis, and (10) treatment.

Pathology.—In summarizing the anatomic and histopathologic features of

chronic pancreatitis, one is particularly impressed by two rather constant findings—interstitial fibrosis and residual necrosis of tissue. The former was present in all cases. Interlobular fibrosis was more pronounced than intra-lobular fibrosis and both were associated with extensive atrophy of the parenchyma. Whether the fibrosis represents a continuing chronic process of inflammation or the regressive and end phase of repeated attacks of acute inflammation is difficult to say from the histologic appearance alone. When the histologic features are studied in the light of the known clinical facts regarding the course of the disease, it seems likely that the latter interpretation is the correct one for most of the cases.

In those cases in which one can exclude the presence of regions of necrosis in the entire pancreas (of which case 16 is an example) it would seem logical to attribute the interstitial fibrosis and atrophy of the parenchyma to repeated attacks of acute interstitial inflammation of the type described, among others, by Archibald (8), by Stetten (9), by Elman (10) and by Gray, Probststein and Heifetz (11).

In those cases in which necrosis of tissue occurred, the inflammatory process probably was closely related to so-called acute hemorrhagic pancreatitis. In other words, we were probably dealing with repeated sublethal attacks of acute hemorrhagic pancreatitis with necrosis. For reasons not well understood at the present time, the inflammatory and necrotizing process in these cases subsided and allowed time for fibrosis and atrophy to occur. In this connection, it may be said that the pseudocysts which were found in these cases were interpreted as the result of acute inflammation, necrosis of tissue and the subsequent digestive action of liberated pancreatic enzymes. Whether obstruction of pancreatic ducts played a rôle in the production of pseudocysts is problematic.

The perineural distribution of lymphocytes which was observed in four cases is interesting in view of the fact that abdominal pain is such a prominent feature in these cases. Perhaps actual involvement of the nerves in the inflammatory process is responsible for the intense pain from which these patients suffer.

The fact that moderate to severe arteriosclerosis was present in six of the ten cases in which tissue was available for study is interesting also, in view of the fact that some workers attribute an important etiologic rôle to vascular occlusion in cases of acute pancreatic necrosis and hemorrhagic pancreatitis. In our cases, however, the arterial changes were interpreted as a result rather than as a cause of the pancreatic lesion. In our opinion, the thickening of the arterial walls was probably the result of atrophy of disuse and represented changes similar to those which occur in the senile uterus.

In summary, chronic relapsing pancreatitis may represent the summation

of repeated attacks of acute interstitial pancreatitis or repeated sublethal attacks of so-called acute hemorrhagic pancreatitis, or, perhaps in some cases, a combination of both types of pancreatitis.

Incidence, onset and precipitating factors.—Chronic relapsing pancreatitis begins most often in the third or fourth decade, but may begin in childhood or old age. It occurs more often among males than among females (ratio 6.2:1.0). It does not exhibit a predilection for obese persons and obesity does not appear to be an etiologic factor. Alcohol and dietary indiscretions at times appear to precipitate the acute attacks. In some instances a long history of alcoholism antedates the first acute seizure. The beneficial effects of internal and external drainage of bile recall the etiologic hypothesis, commonly referred to as the common channel hypothesis, as explaining the possible causation in some cases. The frequent failure to recover bacteria in cultures of bile from the common duct at the time of operation in these and other cases tends to discount the hypothesis of infection due to bacteria. In three out of four cases of this series in which cultures were made of the bile or from the pancreatic region, bacteria were not found.

The onset of chronic relapsing pancreatitis is usually abrupt, with an acute painful seizure. In some cases, painful or painless dyspepsia, even of many years' duration, may precede the first painful seizure. The relationship of these symptoms to the disease is sometimes doubtful. It is possible that some are functional.

Painful exacerbation.—The acute painful exacerbation rarely leaves doubt that organic disease has made its appearance. It usually is of two or more days' duration and rarely of a few hours' duration (table 1). It may last from twenty-eight to thirty-five days. The pain usually is epigastric and may involve the right, middle or left portion of the epigastrium or some combination thereof. Usually the distress penetrates to the back at the level of the thoracolumbar junction, in the midline or to the right or left of the midline, or across the back at this level. If the pain is located in the right portion of the epigastrium anteriorly, it is also usually felt on the same side posteriorly. At times the pain may spread all over the abdomen and lower part of the thorax anteriorly or to the regions of the shoulders.

The pain may be sudden in onset or termination but most often it begins mildly, gradually reaches a plateau and then decreases gradually in severity. The pain ordinarily is constant but there may be superimposed waves of increased intensity. The severity of the pain is indicated by restlessness and profuse perspiration and by the fact that drugs other than opiates rarely give satisfactory relief. When the pain is most severe, opiates may give only partial relief. Opiates do not terminate an attack, as they so often do in cases of uncomplicated biliary colic. Thus, the pain recurs as the effect of the drug

wears off. The position assumed by some patients is often suggestive. The patient sometimes finds partial relief by assuming the sitting posture with the trunk flexed forward and pressure exerted against the abdomen. The distress most often is described as a steady pressure, burning or aching pain, and less frequently as a cramp. These painful exacerbations may occur at long or short intervals; they may be so frequent that the pain becomes almost continuous. The patient may then become a nervous wreck and as a result morphinism or alcoholism may add its devastating effects to an already desperate situation.

The acute painful exacerbation may be accompanied by jaundice, fever, chills and sweating. A peculiar cyanosis may be noted. Abdominal distention may be conspicuous and raise the question of intestinal obstruction. Tenderness is almost invariably present and is usually maximal in the region of maximal pain. Muscular spasm commonly is present but boardlike rigidity such as is characteristic of a perforated viscus is rarely observed. Occasionally, a mass may be felt in the upper part of the abdomen. Shock may appear but usually only in the most severe attacks and when there is extensive pancreatic necrosis. A rapid sedimentation rate and hyperbilirubinemia are often found. Leukocytosis may or may not accompany these attacks.

Sequelae due to involvement of the pancreas. Temporary disturbance of function of acinar cells.—The activity of the enzymes (amylase and lipase) in the serum is increased early in the attack (6, 12–15). High values have been obtained an hour after the onset of pain. Activity of enzymes in the serum reaches a maximal level early, is usually persistently increased throughout the attack and rapidly returns to normal after the attack ceases. Curiously, the activity of both enzymes has not always been found to be increased simultaneously. Sometimes one or the other, and at times both, may be increased. Values may remain continuously elevated when the attacks, even though mild, follow one another in rapid succession or when pancreatitis is active for long periods. Such elevations are conveniently thought of as due to hypersecretion of the acinar cells but often they are undoubtedly due to obstruction of the acinar cells but often they are undoubtedly due to obstruction of the pancreatic ducts, which rupture and thus permit entrance of the pancreatic juice into the lymphatics.

The acute exacerbations may affect the components of the pancreatic juice temporarily. If the disease is mild or moderately severe, the secretion of amylase may be reduced temporarily without reduction of secretion of trypsin or bicarbonate or of the volume of secretion (16).

Permanent disturbance of function of acinar cells.—Progressive destruction of the acinar tissue, either by repeated mild to moderately severe exacerbations, or by one or more severe exacerbations, sooner or later has two results. First, the activity of the enzymes in the serum does not rise with the acute

exacerbation, indicating that normal acinar cells are not sufficiently numerous to provide enough secretion for a rise. Second, external pancreatic secretion is affected progressively with resultant effects on digestion and absorption. After stimulation with purified secretin, secretion of amylase, later of lipase and trypsin, and finally of water and bicarbonate is greatly diminished. Digestion of fats and proteins is affected particularly and varying percentages of the intake of these foods are lost in the feces. The appearance of steatorrhea indicates extensive parenchymal damage. The percentage of ingested foods lost in the stool commonly is less than that resulting from total loss of external pancreatic secretion following partial or complete pancreatectomy in man (17). Stools are typically bulky and fatty in appearance. Liquid fat is fairly commonly found floating on the water of the toilet. One patient described this as resembling the "grease on chili." Stools may be frequent. Their frequency appears to be due, in part, to their bulkiness, because, by restricting the intake of fat and in turn reducing the bulkiness of the stool, one can reduce the number of stools. However, the bulkiness of the feces and their content of undigested and unabsorbed fat and protein are not the only causative factors in the frequency of the bowel movements, because patients who have complete loss of external pancreatic secretion usually have only one or two or three stools a day and not five or ten as may be the case in chronic relapsing pancreatitis.

Temporary disturbance of internal secretion of the islet cells.—Temporary disturbance of internal secretion of the islet cells occurs much less frequently than transitory disturbances of internal secretion of acinar cells. Such disturbance was indicated by transitory glycosuria, hyperglycemia and positive results of glucose tolerance tests.

Permanent disturbance of internal secretion of islet cells—Frank, permanent hyperglycemia has developed in about a fourth of the cases studied. The appearance of pancreatic diabetes denotes extensive destruction of the pancreas.

Palpable epigastric masses.—Such masses may be the enlarged indurated pancreas or pancreatic cysts.

Formation of stones in the pancreatic ducts or calcification in the parenchyma.—Pancreatic stones or calcified regions are found by roentgenologic examination in about 50 per cent of cases. Calcium is considered to be deposited in three possible ways; namely, in regions of fat necrosis, in regions of degenerative tissue and directly in the pancreatic ducts. The deposition of calcium may be localized or it may be widespread throughout the organ to such a degree that the pancreas is clearly outlined in the roentgenogram. On the roentgenogram, the calcification may appear as conglomerate areas or fine punctate shadows of increased density. There may be only three or four fairly large shadows, especially if they are produced by calculi in the ducts of Wirsung or Santorini. Calcification has been noted as early as one year after the first

acute attack. On the other extreme, in one case, calcification was absent fourteen years after onset of the acute seizures but was present five years later.

The question may well be asked, Are the stones secondary to the inflammation or are the attacks of pancreatitis due to obstruction of pancreatic ducts by the stones? We believe that the stones are usually the result and not the primary cause of the disease. This belief is supported by the cases in which calcification occurred while the patients were under observation, as in cases 24 and 26 of this series and in other cases. Stones, once formed, may well produce obstruction with secondary dilatation of the ducts. The stones are usually small, are widely located in the smaller radicles of the ductal system of the pancreas and are consequently difficult to remove surgically. Occasionally, the stones are localized and can be removed by partial pancreatectomy. Rarely, the stones appear to be large and localized in the head of the pancreas or even in the main ducts near their entrance into the duodenum and can be removed by pancreatolithotomy. Cases 17 and 25 of this series illustrate this. Often, however, this tendency to localization in the larger ducts is more apparent than real.

Sequelae arising from pressure of the enlarged pancreas on neighboring structures.—The pancreas, enlarged by the inflammation, may press on the duodenum with partial or complete obstruction, dilatation of the duodenum above the obstruction and dilatation of the stomach with retention vomiting. The obstruction of the duodenum may occur in the second or third parts. Even the jejunum may be obstructed, as it was by a cyst in case 6. Gastroscopic examination may disclose that the enlarged pancreas is displacing the posterior wall of the stomach anteriorly.

Fairly frequently the diseased pancreas produces obstruction of the common bile duct, with thickening and dilatation of and stasis in the duct, biliary tree and gallbladder. With pressure gradients in the biliary tree thus disturbed, it is easy to understand the resulting enlarged, inflamed gallbladder, ascending cholangitis and hepatitis. A condition favoring the formation of gallstones is created. We purposely omitted from this study all cases of chronic pancreatitis in which there was associated cholelithiasis. Chills, fever and jaundice are common symptoms during the acute attacks. When the obstruction is chronic, the jaundice may be chronic.

Enlarged superior mesenteric and splenic veins have been noted by the surgeon and have involved a definite surgical risk in carrying out partial or total pancreatectomy. It may be presumed that the enlargement of the veins is due to pressure of the enlarged pancreas. Splenomegaly (chronic passive congestion) may well be due to partial obstruction of the splenic vein. One could readily visualize how gross gastro-intestinal hemorrhage could occur if one of the varicosities should rupture into the intestinal tract.

Sequelae resulting from involvement of neighboring organs by the disease.—Gastro-intestinal involvement is common. There may be pathologic evidence of direct extension of the process to the stomach and duodenum as gastritis and duodenitis. More often, there is disturbed gastro-intestinal motility. Thus, delayed motility has been noted, as evidenced by the presence of retained food in the gastric contents and by retention of barium in the stomach for twenty-four hours and even longer, when no organic obstruction could be demonstrated. A common cause of failure to obtain a satisfactory test of pancreatic function, using secretion as a stimulant, is the presence of food in the stomach and duodenum after an all-night fast. Slowed motility of the small bowel is observed fairly commonly at roentgenologic examination. During the acute attacks temporary ileus may appear, sometimes most conspicuous in the upper part of the abdomen and suggesting obstruction of the bowel. Too frequently, exploration may be performed as a result of the erroneous diagnosis of intestinal obstruction. Increased motility has also been noted. Disturbances of motility often are presumably neurogenic and due to involvement of the neighboring sympathetic nerves. These disturbances of motility cause nausea and fullness, which may precede actual vomiting. Fullness and heaviness after meals often occur and epigastric burning and abdominal cramping are common. During the acute exacerbations constipation is common, but diarrhea may be chronic without or with external pancreatic insufficiency, in which case steatorrhea and creatorrhea may be demonstrated.

Gross gastro-intestinal hemorrhages may occur during or terminate chronic pancreatitis. Sometimes the hemorrhage has followed alcoholic debauches, a fact which suggests alcoholic gastritis as a source. In cases not included in this series, the bleeding has definitely occurred from the duodenum involved by the pancreatitis and has been the cause of death.

Hepatitis sometimes occurs without demonstrable obstruction or dilatation of the common bile duct but most often follows frank obstruction of the common bile duct. Splenomegaly and ascites may be associated. Splenic enlargement may not be associated with known obstruction and enlargement of the splenic veins or with chronic passive congestion. Possible explanations of hepatitis without obstruction of the common bile duct have been alcoholic hepatitis in one case and infiltration of the liver with fat together with a marked deficiency state in a second case. Puruitus may occur.

Casts in the urine, albuminuria and microscopic hematuria are common evidences of renal irritation, most often associated with the acute seizures. Pleuritic effusions have followed acute exacerbations in cases not in this series.

Other sequelae.—Temporary loss of weight during the acute episodes is common. When the acute attacks are frequent, and particularly when steatorrhea and creatorrhea have appeared, the loss of weight is likely to become per-

manent. Frank malnutrition is fairly common and renders the patient susceptible to intercurrent infection. Fatigue and weakness often are severe and nervousness may be extreme. Many patients are temporarily disabled and some eventually become totally incapacitated for work. This incapacity, plus repeated sojourns in the hospital, multiple operations (unfortunately too often for some other suspected disease) and bills for medical care, constitutes a financial burden which many of these patients are unable to meet. The patient thus loses stamina and courage and morphinism may occur. The discouragement may lead to alcoholism in an attempt to find solace and respite from pain.

As a rule, deficiency states do not reach the stage of clinical recognition in cases of chronic relapsing pancreatitis. This is an important point in the differentiation of the two most frequent types of steatorrhea; namely, nontropical sprue and chronic pancreatitis with external pancreatic insufficiency. The concentrations of serum protein, calcium and phosphorus and of plasma lipoids usually remain normal. Occasionally, the concentrations of plasma lipoids and of serum protein may fall below normal range. It is only when severe deficiency states appear that the picture may simulate nontropical sprue. This occurred in only one case of our series (case 16). In this case, in which the patient had familial diabetes with a pancreas presumably hypoplastic, pancreatitis developed. Steatorrhea and creatorrhea became clinically manifest and finally hypolipemia, hypoproteinemia with nutritional edema, hypocalcemia with tetany and hypoprothrombinemia developed. The anemia was of the hypochromic type. The liver became enlarged recurrently. During the periods of hepatomegaly, the hepatic dysfunction was measured by the sulfobromophthalein test. Even a roentgenogram of the small bowel disclosed the picture of a deficiency state. This case is the only one in our experience in which the picture has simulated nontropical sprue sufficiently to cause any confusion. Peripeheral neuritis may occur, as in case 28 of our series, and probably is primarily due to dietary deficiency.

Anemia of the hypochromic type is fairly frequent. It has been macrocytic only in the presence of hepatic disease.

Terminal aspects.—The patient who has chronic relapsing pancreatitis can tolerate diabetes and steatorrhea well, particularly since replacement therapy can adequately control these sequelae of the disease. However, he cannot tolerate the attacks of pain, especially when they become frequent and severe, without serious impairment of his health and morale. It is of special interest, therefore, to recognize that the disease may become painless. This may happen after a few attacks or after many years of painful episodes, before or after appearance of calcification, steatorrhea, creatorrhea and diabetes. Failing this, the attacks may at least become less frequent and less severe, so that

they grow more bearable. Progression of the disease does not necessarily cease after the cessation of pain, for major disturbances of function may appear after the disease has become painless or relatively painless. In fact, it must be remembered that, in some instances, the disease apparently may be painless or relatively so even in the face of its steady progression over the passing years. Moreover, severe disability with nervousness, fatigue and lack of stamina may persist in spite of cessation of pain and regardless of replacement therapy.

To date seven of the twenty-nine patients of this series have died. Death may be due to pancreatitis, to its sequelae or to other diseases. Cerebral hemorrhage has been responsible for death in two cases, carcinoma of the lung in one and leakage at the cholecystogastric stoma with resultant peritonitis and formation of abscess in another. In still another case, death followed peritoneoscopy. One patient died of an acute respiratory infection; one of pylephlebitis, thrombosis of the portal vein and multiple hepatic abscess in association with an attack of hemorrhagic pancreatitis. In cases not of this series, death has been due to hemorrhagic necrosis, gross gastro-intestinal hemorrhage or tuberculosis.

Diagnosis.—The diagnosis of chronic relapsing pancreatitis is made in the following steps. First, chronic pancreatitis is suspected because of the history and perhaps because of physical findings. If these are sufficiently typical of pancreatitis, the diagnosis may be established on this basis alone. Second, the existence of disease of the pancreas is proved by the response to tests of pancreatic function and by roentgenograms of the pancreatic region for calcification. Third, if pancreatitis is present, the primary nature of the disease is then proved by the exclusion of diseases of neighboring organs capable of producing pancreatitis. This is not always possible. Fourth, when the presence of pancreatic disease cannot be demonstrated by appropriate tests, the diagnosis still can be made by the combined procedure of excluding disease capable of simulating pancreatitis and obtaining a history compatible with or typical of pancreatitis.

The diagnosis of the fully developed syndrome of chronic pancreatitis is a simple matter. A history of recurring attacks of severe pain in the upper part of the abdomen during the course of which there occur diabetes and diarrhea characterized by bulky, fatty-appearing stools, permits the diagnosis of chronic pancreatitis on this basis alone with a high degree of certainty. When the attacks of epigastric pain have been frequent and of several days' duration, and when the pain and soreness have occurred in the left portion of the epigastrium and left costovertebral angle, the diagnosis is even more certain. The demonstration of pancreatic calcification by roentgenologic examination and of an excessive amount of fat (more than 10 per cent of intake) and nitrogen (more than 2 gm. daily) in the stool clinches the diagnosis. Demonstra-

tion of deficiency of external pancreatic secretion after stimulation with purified secretin or mecholyl chloride adds another bit of definite evidence but this is not necessary in the fully developed syndrome. Disease of the biliary or gastro-intestinal tract usually can be excluded by the history and appropriate laboratory procedures but when chronic jaundice is present, exploration may be the only measure that will settle the question whether or not disease of the biliary tract also is present.

Few uncertainties of diagnosis exist even in those legs completely developed syndromes of chronic pancreatitis in which recurring attacks of pain are coupled with only one or two of the three sequelae most diagnostic of chronic pancreatitis; namely, diabetes, steatorrhea and pancreatic calcification. The combination of recurring attacks of pain in the upper part of the abdomen with steatorrhea or pancreatic calculi leaves little reasonable doubt about the existence of chronic relapsing pancreatitis. On the other hand, the co-existence of recurrent attacks of pain in the upper part of the abdomen and diabetes leaves some doubt at times because diabetes may have antedated the onset of the painful seizures. Diabetes is of greater diagnostic importance when a family history of diabetes mellitus cannot be obtained, when it is known that the patient was not diabetic before the onset of acute episodes of pain and when the diabetes appears during or soon after an acute attack. Sometimes a diabetic type of glucose tolerance test curve may be the sole evidence of diabetes. If so, it should be used in diagnosis only with due recognition of the occurrence of false positive curves.

The greatest difficulty in diagnosis lies in those cases in which the sole manifestation of the disease is recurrent attacks of epigastric pain. The frequency with which the diagnosis is made in such cases will depend largely on the clinician's awareness of pancreatitis as a cause of pain in the upper part of the abdomen. Actually, chronic pancreatitis, as well as disease of the biliary and gastro-intestinal tracts, kidneys and heart, should be suspected in every case in which there is a history of recurrent attacks of pain in the upper part of the abdomen. Chronic pancreatitis will be confused with disease of the biliary tract and duodenum most readily when the pain and tenderness have been limited to the right part of the epigastrium and right part of the back, as they were in eight of the twenty-nine cases of this series (cases 3, 9, 12, 13, 19, 20, 25 and 27).

Chronic relapsing pancreatitis should be more frequently suspected when the pain and tenderness involve the left part of the epigastrium and left part of the back, or the left as well as the right part of the epigastrium, than when they involve only regions to the right of the midline, because uncomplicated cholecystic disease rarely causes pain and tenderness to the left of the midline. Regardless of the location of the pain, chronic pancreatitis should be suspected, along with other complications of cholecystic disease, when the attacks have

lasted more than a few hours, when the pain has repeatedly recurred after hypodermics of morphine and when the pain has been steady and gradual in development and cessation. The duration, severity and location of the pain will serve to distinguish it from the usual biliary colic. A cholecystogram showing a functioning gallbladder and no stones usually may be interpreted to mean that cholecystic disease of a degree sufficient to cause seizures typical of pancreatitis does not exist. Hydronephrosis, duodenal ulcer and intermittent intestinal obstruction are excluded by a carefully taken history and appropriate laboratory tests. Given a history of recurring attacks of pain in the upper part of the abdomen compatible with or typical of chronic pancreatitis in a case in which diseases of the biliary and gastro-intestinal tracts, kidneys and heart have been excluded with reasonable certainty, the diagnosis of chronic relapsing pancreatitis can be made with a high degree of accuracy. It is recognized that under these conditions the diagnosis of chronic pancreatitis remains presumptive and that the diagnosis may be made with certainty only by exploration or by awaiting an acute attack when transitory disturbances of function may be demonstrated by appropriate tests of pancreatic function.

Chronic relapsing pancreatitis is most likely to be overlooked when the pain is mild. In such cases, the diagnosis probably will be made only if steatorrhea has appeared, if a cholecystogram taken to exclude cholecystic disease discloses pancreatic calculi or if a test for activity of enzymes in the serum to exclude pancreatitis shows them to be increased. It is these rare and unusual cases of painless or relatively painless pancreatitis that permit understanding of the occasional case of pancreatic calcification in which a history of pain cannot be obtained. However, because calcification in the region of the pancreas in a case in which pain has not been a feature is frequently not due to pancreatitis, a diagnosis of pancreatitis should not be made hastily unless the distribution and appearance of the calcification are distinctly characteristic or unless steatorrhea or diabetes is likewise present.

The diagnosis of chronic relapsing pancreatitis during acute exacerbations of the disease rests largely on the same historical and laboratory data as are used for diagnosis in the interval between the attacks. However, the diagnosis often is made with greater ease during the acute exacerbation than it is during the interval between attacks, especially when steatorrhea, diabetes and pancreatic calculi have not developed. This is so because it is possible to ascertain with great accuracy the location, character and extension of the pain and the location of the points of tenderness on the basis of which the diagnosis may be suspected, and because the existence of pancreatic disease may be proved by demonstrating transitory disturbances of pancreatic function. Thus, transitory increase of activity of enzymes in the serum will be found as long as functioning acinar tissue remains in amount sufficient to produce the enzymes. Transitory glycosuria and hyperglycemia likewise may be found if the islet

cells are sufficiently attacked by the disease. On the other hand, it is often necessary to await the termination of the acute attack, improvement in the general condition of the patient and disappearance of the jaundice and of hepatic dysfunction before satisfactory roentgenologic examination of the pancreas, gallbladder, stomach and duodenum can be carried out for the purpose of demonstrating pancreatic calculi and of excluding other abdominal diseases capable of simulating and even causing pancreatitis. Fortunately, the condition of the patient rarely is such that operation may not be delayed long enough to permit one to establish the diagnosis. Even if disease of the biliary tract is ultimately found, the surgical risk is less if the process in the gallbladder and pancreas has been allowed to subside than if operation is performed before the end of the attack.

When the biliary tract has been obstructed and changes secondary to pressure have occurred in consequence of enlargement of the pancreas, the primary character of the pancreatitis may be missed and the pancreatitis ascribed to disease of the biliary tract. In such cases, the cholecystogram may show the gallbladder to be nonfunctioning and yet the surgically removed gallbladder may show only minor degrees of disease incapable, in our opinion, of producing the syndrome of chronic relapsing pancreatitis. Likewise, the patient's illness may be misinterpreted and attributed to duodenal ulcer when a duodenal deformity secondary to the pancreatitis or to adhesions from adjacent structures is interpreted as an ulcer by the roentgenologist and the clinician.

Perforated peptic ulcer and intestinal obstruction are the most frequent conditions with which the acute exacerbation of chronic pancreatitis is confused. When frequent attacks of pain have occurred in the past, the temptation to perform emergency exploration for perforated peptic ulcer will be lessened if a careful history and physical examination are obtained, if more frequent use is made of the determinations of values for amylase in cases of acute abdominal emergency or of intestinal obstruction, and if more frequent use is made of intestinal deflation by tube in cases in which intestinal obstruction is suspected.

Diseases other than those of the biliary and intestinal tracts and kidneys must be distinguished from chronic relapsing pancreatitis. Fairly frequently, carcinoma of the pancreas or of the ampulla of Vater may cause attacks of pancreatitis indistinguishable clinically and even at operation from those of primary chronic pancreatitis. Usually the progressive nature of the disease in such cases soon renders the diagnosis clear.

Less often, retroperitoneal tumors produce painful attacks, which simulate those of chronic pancreatitis in their course and in the location and severity of pain. The failure to demonstrate elevated values for enzymes during the acute episodes is helpful in distinguishing the two diseases from one another. The excretory urogram, by demonstrating that a kidney is displaced by a retroperitoneal process, may permit diagnosis of a retroperitoneal neoplasm.

Another disease occasionally considered in differential diagnosis is nontropical sprue. Confusion between the two diseases may arise when chronic relapsing pancreatitis has produced steatorrhea. Actually, there is little reason for confusion, for the similarity of the two diseases usually ends with the steatorrhea. Nontropical sprue usually presents one or more of the following features: (1) macrocytic anemia, (2) hypoproteinemia with nutritional edema, (3) hypocalcemia with tetany and osteoporosis, (4) hypoprothrombinemia with or without a tendency to bleeding. On the contrary, chronic relapsing pancreatitis is usually not associated with macrocytic anemia except when chronic hepatitis is present. Hypoprothrombinemia occurs in both diseases but in pancreatitis it occurs only in the presence of jaundice and hepatic disease. In our experience, hypocalcemia has occurred in only one case of chronic pancreatitis and hypoproteinemia is almost as rare. In fact, as we have pointed out previously, only one patient who had primary chronic pancreatitis has presented the picture of a deficiency state such as that observed in cases of nontropical sprue, and this case was unusual in that the boy had diabetes of great severity and pancreatitis appeared to have been superimposed on—pre-existing pancreatic hypoplasia. It is our belief that the deficiency state developed in this case chiefly because of the diabetes, the pancreatic atrophy and the demands of growth, rather than because of the pancreatitis. In the presence of such evidences of a deficiency state, the diagnosis of pancreatitis should be made with great caution.

Similarly, chronic pancreatitis presents findings not encountered in cases of sprue. Jaundice, diabetes and pancreatic calcification commonly occur in cases of pancreatitis but almost never in cases of nontropical sprue. The pain of pancreatitis rarely should be confused with that of nontropical sprue. Moreover, when steatorrhea is present in a case of pancreatitis it is usually associated with calculi or diabetes, or both. In the presence of these complications of pancreatitis, the diagnosis of nontropical sprue should be made with extreme reluctance.

The roentgenologic examination of the small bowel may disclose the so-called deficiency pattern in both diseases and cannot be depended on to distinguish them. The amounts and types of fat and the amount of nitrogen in the stools may be so similar that analysis of stools is not a reliable measure of differential diagnosis. The secretin test of pancreatic function may disclose some diminution of pancreatic secretion in cases of nontropical sprue but, whereas in cases of pancreatitis profound diminution of external pancreatic secretion, of a degree sufficient to produce steatorrhea, may be observed, this rarely, if ever, occurs in cases of nontropical sprue.

Treatment.—Chronic relapsing pancreatitis may be treated medically or surgically, or by a combination of these methods.

Medical treatment is purely palliative and consists in relief of pain, treat-

ment of dyspepsia and substitution therapy in those cases in which there is demonstrable pancreatic insufficiency. Treatment of the acute exacerbation is primarily medical. Opiates are usually required in order to relieve distress. Ephedrine and related compounds have been used with some apparent success, while glyceryl trinitrate and allied drugs sometimes have given fleeting relief. Intravenous and subcutaneous administration of fluids may be necessary because of the vomiting and dehydration. If abdominal distention occurs, the intestinal tube with suction is valuable. Shock, when present, is treated by accepted methods.

Satisfactory medical measures for prevention of attacks do not exist but, since alcohol may be an aggravating factor in some cases, abstinence is advised. Many patients are intolerant to rich, fatty foods and for that reason a bland diet relatively low in fat is indicated.

Medical treatment of the sequelae of chronic pancreatitis consists in dietary measures and replacement therapy. Control of the diabetes needs no comment here. Diarrhea is satisfactorily controlled by limiting fat content of the diet to 100 or even 50 gm. a day and by giving pancreatin in enteric coated tablets in doses of 2 to 10 gm. three times a day. Malnutrition is prevented by a high caloric intake and administration of pancreatin. The slight possibility of hypoproteinemia is adequately prevented by a high protein content in the diet (100 gm. or more) with or without pancreatin. Mild anemia may require iron therapy and gross hemorrhage may require transfusions. Roentgen therapy may be administered for chronic pain but it does not often produce benefit.

The possibility of deficiency of lipocaic must be borne in mind until it is definitely proved that lipocaic is or is not a secretion of the pancreas. If deficiency of lipocaic occurs, it must be rare.

Indications for surgical treatment are several. Chronic duodenal obstruction requires gastro-enterostomy and even partial pancreatectomy. Chronic obstruction of the common bile duct requires cholecystogastrostomy, choledochostomy, choledochoduodenostomy or cholecystostomy. Pancreatic cysts require either internal drainage into the stomach or duodenum or external drainage with marsupialization. Pancreatic abscess requires external drainage. Recurrent gross gastro-intestinal hemorrhage may need partial gastrectomy. Pancreatolithotomy is indicated for the relief of the obstruction of a pancreatic duct when the obstructing calculi for the most part are limited to the larger ducts of the head of the pancreas.

For the chronic disability and invalidism from severe persistent pain, any surgical procedure that promises relief is worth a trial. The procedures most commonly resorted to are those designed to drain the bile externally (cholecystostomy, choledochostomy or both) or internally (cholecystogastrostomy, cholecystojejunostomy or choledochoduodenostomy) in order to reduce the

pressure in the common bile duct. Any and all of these procedures have been followed by complete or partial remission of the recurring exacerbations of pain and should be resorted to before more radical procedures are carried out. Internal drainage or external drainage of cysts with marsupialization likewise may be followed by complete or partial relief from the pain. Pancreatolithotomy has also been followed by satisfactory relief. These surgical measures do not always result in satisfactory remission but remissions have been frequent enough and of sufficient duration to justify their employment for relief of pain and the resulting invalidism and disability. Even in the early stages of the disease a trial of surgical treatment is worth while in the hope of preventing the sequelae and disability of pancreatitis. More radical surgical procedures are clearly indicated when the more conservative measures have failed but only when the pain is disabling. Partial pancreatectomy may be done when the disease is limited chiefly to the head or tail, and total pancreatectomy when the entire pancreas is affected severely. Such procedures have not been carried out in cases of this series but have been done with encouraging results on a few patients seen in the years 1944 and 1945.

CONCLUSIONS

On the basis of analysis of the clinical, clinicopathologic and pathologic data on a series of twenty-nine cases of chronic relapsing pancreatitis without associated disease of the biliary or gastroduodenal tracts of a degree sufficient to influence the clinical picture the following conclusions are drawn:

1. Chronic relapsing pancreatitis appears to represent the summation of repeated attacks of acute interstitial pancreatitis or repeated sublethal attacks of so-called acute hemorrhagic pancreatitis or a combination of the two types of pancreatitis. Interstitial fibrosis and residual necrosis and atrophy are the constant chronic changes. Regions of calcification or stone, pseudocysts and abscess are less frequent but striking residua.

2. Chronic relapsing pancreatitis characteristically is a disease of recurring acute exacerbations separated by short or long intervals of relative clinical quiescence. During the early stages of the disease, the clinician may not be able to demonstrate existence of pathologic physiologic changes by physical or laboratory methods of examination; yet the surgeon or the pathologist will be able to demonstrate pathologic changes in the organ. However, later in the course of the disease, the destruction of the pancreas will reach the point where disturbances of internal and external secretion, pancreatic calcification and other sequelae will be demonstrable at all times.

3. Chronic relapsing pancreatitis characteristically manifests itself by recurring prolonged attacks of severe pain in the upper part of the abdomen, by disturbances of function of the acinar and islet cells and by certain sequelae. Disturbances of function may be transitory and mild during the acute episodes

before widespread anatomic destruction has occurred. These disturbances are demonstrated by appropriate laboratory tests. When destruction of the acinar and islet cells has become sufficiently extensive, glycosuria and hyperglycemia, steatorrhea and creatorrhea appear and persist. Pancreatic stones or calcification appears in roentgenograms of the organ and the enlarged organ and cysts may be felt.

4. The clinical picture of chronic relapsing pancreatitis is due not only to disease in the pancreas but also to the effect of the disease on neighboring organs including the stomach, duodenum, small bowel, liver, biliary tract and blood vessels. The most striking of these sequelae are obstruction of the common bile duct, jaundice, hepatitis, distention of the gallbladder and obstruction of the duodenum.

5. The diagnosis of chronic relapsing pancreatitis should be made with a high degree of accuracy, because of the highly characteristic clinical picture, including the characteristic painful exacerbations and the disturbances of function of the pancreas demonstrable during and between the acute exacerbations.

6. The treatment of choice of chronic relapsing pancreatitis is surgical. The results of conservative surgical procedures (internal or external drainage of the biliary tract and of pancreatic cysts, pancreatolithotomy or gastro-enterostomy for duodenal obstruction) are sufficiently good to warrant frequent and early use. Radical surgical procedures (partial or total pancreatectomy) may be utilized if the conservative ones have failed and then only for relief of persistent and disabling pain. Medical measures include (1) diet and replacement therapy (insulin and pancreatin) for control of diabetes and steatorrhea; (2) drugs for control of pain, and (3) supportive measures in case of shock.

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HISTAMINE STIMULATED FRACTIONAL GASTRIC ANALYSES: THE DIAGNOSTIC VALUE OF TOTAL SECRETION¹

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EDITORIAL NOTE

When this paper was submitted, the Editor wrote Dr. Glenn expressing regret that in the conclusions he had not come out flatfootedly and said that his data agreed with those of Vanzant, Comfort and others in showing that there is no sense in trying to diagnose duodenal ulcer with the help of gastric analysis because there isn't enough difference between the distributions representing the data from normal men and men with ulcer. The Editor remarked that gastro-enterologists would probably go on for 100 years trying to perform the impossible because they had been brought up to so trust in the results of gastric analysis that they couldn't easily change their habits, but that after one glance at the graphs in this paper, no trained statistician would ever want to pump a stomach for the diagnosis of ulcer; he would see so clearly that he was "licked before he started."

Later, Dr. T. C. Barnes, Dr. Glenn's friend, wrote to say that Glenn had sent his data to a statistician who wrote back saying just what the Editor had said; namely, that although there were small differences in the distributions of data from controls and patients with ulcer, and although, on the average, gastric acidity and volume of secretion are slightly greater in patients suffering from ulcer than in controls, there is so much overlapping of the distributions that only rarely if ever could one say from a single datum that the individual concerned had or did not have an ulcer.

Most unfortunately, poor Dr. Glenn was by that time on his death bed, and before he could make the changes in his "conclusions" he passed away. We regret greatly that this fine physician failed to live to see his excellent paper in print. We are happy to publish it here, and we hope that it will have the influence on the practice of gastro-enterology that it deserves to have.—Ed.

INTRODUCTION

The presence of free acid in stomach contents is generally accepted as a necessary factor in the genesis of duodenal ulcer. Most gastroenterologists are loathe to accept a diagnosis of active duodenal ulcer when no free acidity is present. However, it is probably also a prevailing opinion among these same men that the measurement of gastric acidity, as done by the presently accepted,

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most popular method, that is, the fractional analysis using histamine as a stimulant, is of no value in aiding the diagnosis of duodenal ulcer.

The histamine stimulated fractional gastric analysis as usually done takes into consideration only the level of the acidity, and disregards the total amount of contents at this acidity level. This is usually the case because of the difficulties in obtaining the total contents. However, Polland (1) in one of his early reviews of the histamine gastric analyses in which he considered both the volume and acidity, felt that the total gastric secretion was of value in differentiating normal patients from those with ulcers, and especially in differentiating between benign and malignant lesions. Others (2), (3) felt that the variations found were not of particular diagnostic significance. In view of this difference of opinion it was felt that a further study of this question could be made, particularly in the limited age group afforded by soldiers so that the variations of age encountered in the other studies were not a complicating factor.

Gastric analyses of ulcer patients are usually compared with gastric analyses of normal individuals in attempting to make a differential diagnosis. It may be, however, that this comparison is not the most valuable one; but the comparison should be made with other patients who are complaining of similar digestive symptoms. After all, whenever a differential diagnosis of duodenal ulcer arises, the diagnosis of "normal" is not one of the diagnoses entertained. We cannot feel that a patient is "normal" if he is complaining of digestive symptoms, even if our findings are entirely negative and the symptoms are felt to be entirely functional in origin.

METHOD OF STUDY

Any study to be of practical value should be easily performed in any doctor's office. This report is based on such a practical study. We did fractional gastric analyses using 0.0005 gram of histamine injected subcutaneously as a stimulant. The fasting stomach was entirely emptied and then it was again entirely emptied at 15-minute intervals after histamine stimulation for 4 specimens using 14 or 16 Fr. Levine tube. All available contents were withdrawn with the patient being turned to both sides and his back and the tube moved to several levels in his stomach during the withdrawal. Patients were all in an 11 to 14 hours fasting state from the night before. They did not smoke before or during the analysis and all saliva was expectorated during the analysis. The tests were performed by corpsmen having had various amounts of training under our supervision. However, these men had varying degrees of thoroughness and interest in their work. Of course, no corpsman was kept on this work for any length of time if he was not interested in performing analyses cor-

rectly (4). However, it was impossible to watch all the tests being performed so that it is probable that some were not done exactly as directed. Patients had been seen to be smoking at times. Sometimes, emptying of the stomach was not as thorough as it could have been. In the laboratory no special consideration was given to the gastric analyses. They were done at varying times after completion, though always on the same day. However, the practical consideration is that the tests were done as they might usually be done without the personal handling of the physician. Though errors occurred, the opportunity for their occurrence was of equal degree in both groups of the study, so it is felt that they probably balance each other.

Using this method of collection we have compared the findings in 200 cases of duodenal ulcer with those in 250 control cases. The patients were all soldiers in a general hospital, practically all between the ages of 19 to 30 years.

TABLE 1
Diagnoses made on control patients

Psychoneurosis.....	74	Gastric polyp.....	2
No digestive disease.....	59	Trichuriasis.....	2
Gastritis.....	27	Duodenal diverticulum.....	2
Ill-defined condition.....	20	Asthma.....	1
Constitutional psychopathic state.....	13	Esophageal diverticulum.....	1
Colitis.....	11	Congenital stomach deformity.....	1
Ankylostomiasis.....	11	Hyperchlorhydria.....	1
Hepatitis.....	5	Hiatus hernia.....	1
Constipation.....	5	Sprue.....	1
Gall bladder disease.....	5		
Adult maladjustment.....	4	Total.....	250
Giardiasis.....	4		

The controls consisted of soldiers who had digestive symptoms quite similar to these of the patients in whom a diagnosis of duodenal ulcer was finally made. A duodenal ulcer was considered in differential diagnosis in the control patients but such a diagnosis was not finally made. Such diagnoses as psychoneurosis, or some less critical entity, or no disease of the digestive tract, were made, or the digestive symptoms were felt to be associated with other diseases. These diagnoses are listed in table 1. As previously stated, it is from this group of patients that the differential diagnosis of duodenal ulcer is to be the most valuable.

In the 200 duodenal ulcer cases, the diagnosis was made with the usually accepted diagnostic criteria. Perhaps the one criterion to which most importance was attached was the finding of persistent duodenal bulb deformity by fluoroscopic or by radiographic examination. In only rare instances would

a diagnosis of duodenal ulcer be made if the duodenum was entirely normal by fluoroscopic or radiographic examination.

RESULTS

In comparing the control and duodenal ulcer cases by the usual method of considering the free and total acidity levels, there is only slight difference in the two groups. This is graphically shown in Figure 1 which compares the peak level of free acidity and the peak total acidity in the two groups. The greatest separation in the two groups is in the low acidity range. In the zone below 60 units of free acid (as shown in the tabulation in figure 1A) there were 26.8 per cent of the controls as compared to 13.0 per cent of the ulcers. In total acid peaks, 36 per cent of controls were below 80 units as compared to 17.5 per cent

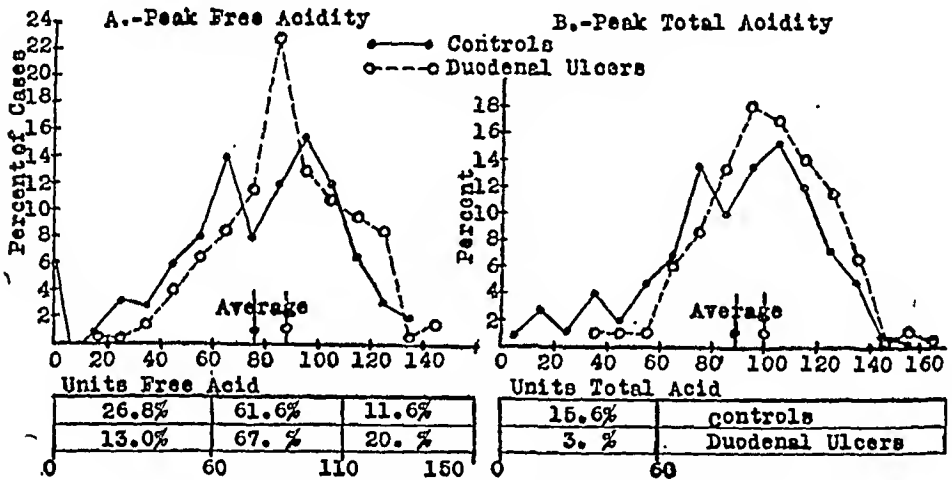


FIG. 1. DISTRIBUTION OF HISTAMINE STIMULATED PEAK ACIDITY

of the ulcers. Below 60 units total acid, however, there were 15.6 per cent of the controls compared to 3 per cent of the ulcers (tabulation in figure 1B). Roughly this means that in only about 25 per cent of the cases is there a 2:1 ratio of distribution between the two groups of cases. This is in accord with the opinion that the histamine stimulated fractional gastric analysis is of little value in the differential diagnosis of duodenal ulcer by this comparison.

The two groups are compared on the basis of difference in the sustained level of acidity to histamine stimulation on the theory that the ulcer patient may respond more quickly or maintain a higher level of acidity for one hour after stimulation. A figure for this comparison is obtained by merely totaling the figures for the free and total acidity respectively for the four specimens obtained after the histamine stimulation. This comparison is made in figure 2. As can be noted, there is a little more separation of the two groups than in com-

paring only the peak acidities (fig. 1), particularly, there is more separation in the higher range than in the previous comparison of peak acidities. As noted in the tabulation for the sum of total acidities, in 47 per cent of the cases a greater than 2:1 ratio of differences between the groups exist. These figures

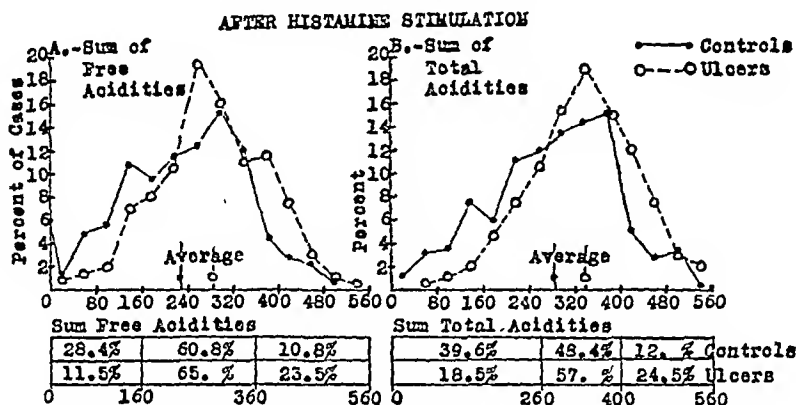


FIG. 2. DISTRIBUTION OF SUM OF ACIDITIES OF 4 SPECIMENS (Q. 15 MIN.) AFTER HISTAMINE STIMULATION

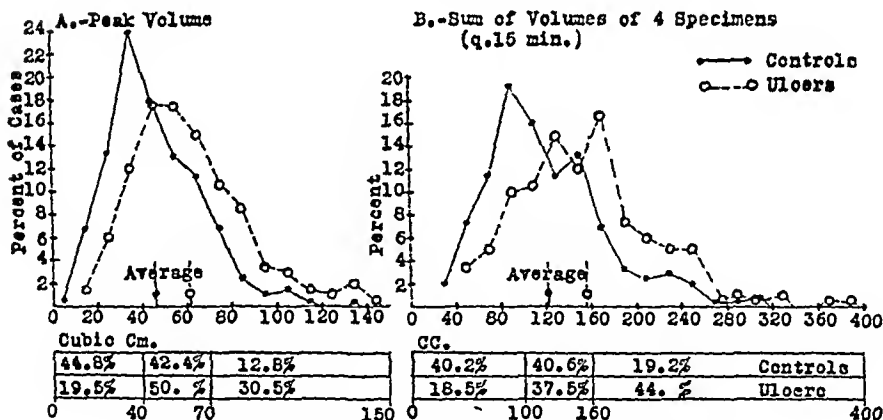


FIG. 3. DISTRIBUTION OF VOLUMES AFTER HISTAMINE STIMULATION

indicate that slightly higher levels of acidity are maintained longer in the ulcer cases.

The next comparison of the two groups is the volume of secretion obtained after histamine stimulation. Figure 3A compares the peak volumes obtained after histamine stimulation. This comparison shows more separation than the comparison of peak acidities. Below 40 cc. peak volume (as shown in the

tabulation in figure 3A), there are 44.8 per cent of the control cases and 19.5 per cent of the ulcers, while above 70 cc. peak volume there are only 12.8 per cent of the controls compared to 30.5 per cent of the ulcers. Roughly, this means that in about 54 per cent of the cases there is well over 2:1 ratio of difference in distribution between the two groups.

Figure 3B, compares the sum of the volumes of the 4 specimens obtained at 15 minute intervals after histamine stimulation. As is noted, about 40 per cent of the cases in both groups fall within the same volume range (100-160 cc.). Below the 100 cc. volume level, however, there are 40.2 per cent of the control cases in comparison to 18.5 per cent of the ulcers, while above the 160 cc. level there are only 19.2 per cent of the control cases compared to 44.0 per cent of the ulcers. This indicates that in 61 per cent of cases there is better than 2:1

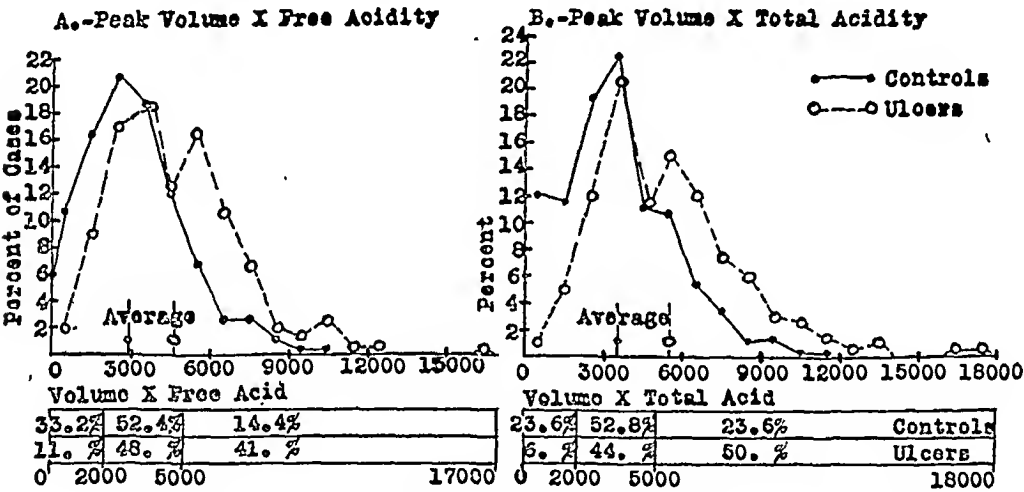


FIG. 4. DISTRIBUTION OF HISTAMINE STIMULATED VOLUME X ACIDITY PEAK

ratio of difference in distribution between the two groups. Figure 3, therefore, indicates that ulcer patients secrete a larger volume than the control patients. In the patients in this study, there is a greater difference between ulcer and control patients when the volume of secretion rather than acidity is compared.

The further comparisons of the two groups take into consideration both the volume as well as the level of acidity after stimulation. Figure 4A shows the distribution of the peak figure obtained from each case by multiplying the volume by the free acidity of each of the 4 specimens after histamine stimulation. Figure 4 B is a similar comparison of peak figures of the volume multiplied by the total acidity figure. As is shown, in the tabulations, however, although about 50 per cent of the cases of both groups fall into the mid-zone, the separation of the two groups in the low and high zones is greater than in any of the preceding comparisons. In the figures for the peak of volume times free acid-

ity, 33.2 per cent of the control cases fall below the figure 2000 in contrast to 11.0 per cent of the ulcers. In the high zone (above 5000), there are only 14.4 per cent controls while 41.0 per cent of ulcers fall in this zone. In the tabulation in figure 4B, the comparisons of the peak figures of volume times the total acidity, the low zone (below the figure 2000) contains 23.6 per cent of control cases in contrast to 6.0 per cent ulcers, while the high zone (above 5000) is 23.6 per cent and 50.0 per cent respectively. Roughly, this means that in about 52 per cent of the cases there is well over 2:1 and almost a 3:1 ratio of distribution between the two groups. In the low range the ratio is 23.6 to 6 or about 4:1 whereas in the high zone it is 50 to 23.6 or over 2:1.

The last comparison between the two groups is to compare them on basis of both the volume and the acidity produced in all four specimens obtained at 15

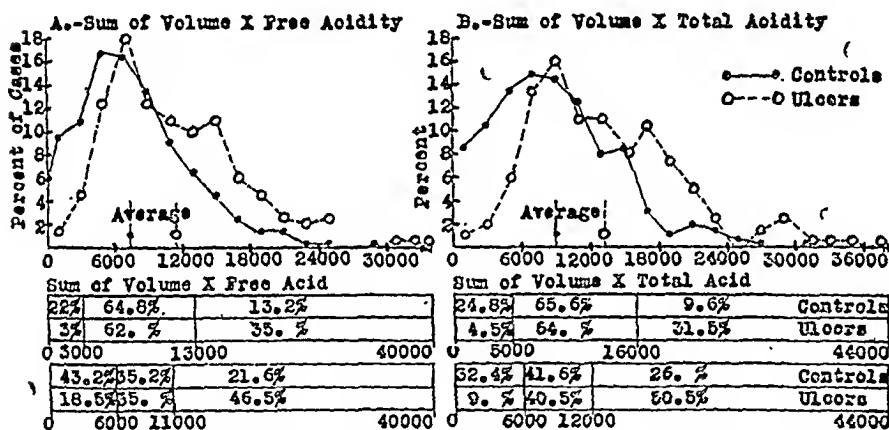


FIG. 5. DISTRIBUTION OF THE SUM OF VOLUME X ACIDITY OF 4 SPECIMENS (Q. 15 MIN.) AFTER HISTAMINE STIMULATION

minute intervals after histamine stimulation. For this comparison the volume of each specimen was multiplied by the acidity, the free and total acidity respectively, and the sum of these 4 figures obtained. This, of course, is again an arbitrarily obtained figure but it can be used as an index for comparison of the total secretion for 1 hour after histamine stimulation.

Figure 5A shows the distribution using the free acidity to obtain this index figure, while figure 5B uses the total acidity. The percentage distribution in the various ranges is indicated in the tabulations in the lower half of the figure. Noting the figures for the sum of volume times free acid, it is seen that in 65 per cent of the cases there is over 2:1 ratio of difference in distribution between the two groups. In the figures for the sum of volume times total acid, this ratio is present in 59 per cent of the cases.

It appears from these figures that the gastric analysis with histamine stimulation can be more helpful in diagnosis of duodenal ulcer, if the volume, in addition to the acidity, is taken into consideration. The comparisons in this study are based on 4 specimens (with complete emptying of stomach) taken at 15-minute intervals after histamine stimulation. It may be that more specimens taken over a longer period would show that higher level of secretion was maintained even longer in ulcer cases.

CONCLUSION

The figures presented indicate that in the two groups of cases, that is, 200 soldiers with duodenal ulcer compared with the 250 control cases with similar digestive symptoms, there is some difference in the histamine stimulated fractional gastric analyses. Little difference is apparent when only the peak stimulated free and total acidity are compared. This is in keeping with the idea that histamine is a maximum stimulant for degree of acid produced and that this acidity reaches a maximum which is attainable in a stomach, frequently regardless of the disease present, as long as the parietal cells are capable of producing acid. However, when comparison is made considering both the degree of acid and volume produced, there appears to be more difference which tends to support the theory of hypersecretion in cases of duodenal ulcer.

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Note: Sgt. John H. Hall, Cpl. Harmon M. Hill, and Cpl. Austin F. Sitler performed most of these tests and their competent work is appreciated. Dr. Robert Parker and Miss Bancroft of the University Hospitals, Cleveland, graciously reviewed the statistical material.

HETEROTOPIC PANCREATIC TISSUE IN THE REGION OF THE PYLORIC ORIFICE¹

A RADIOLOGICAL AND PATHOLOGICAL ANALYSIS OF FIVE CASES OF CLINICALLY SUSPECTED PEPTIC ULCER IN WHICH ONLY PANCREATIC RESTS WERE FOUND

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INTRODUCTION

Since Klob (1) in 1859 first called attention to the aberrant pancreas a considerable amount of medical literature has accumulated on the subject. This was reviewed thoroughly by Poppi (2) in 1935 and again by Faust and Mudgett (3) in 1940. The older articles deal for the most part with the report of the finding of pancreatic tissue in some abnormal site and a great deal of controversy as to the correct embryological explanation. It has been established that in over 70 per cent of these cases the aberrant tissue is located in the wall of the stomach, duodenum or jejunum but many unusual locations such as mesentery, omentum, splenic capsule and gall bladder have been described. As to the cause, no universally accepted explanation has been reached. Most authors agree on some developmental basis, however King and McCallum (4) have advanced the view that the lesions are acquired, usually in adult life, from the surface epithelium as the result of the action of abnormal stimuli.

In later articles more attention has been paid to the various serious pathological conditions which may arise from these anomalies and endanger not only the health but even the life of the individual. Their possible relationship to the development of peptic ulcers in the stomach and duodenum, through the excretion of active pancreatic juice has been stressed. Cases in which malignant tumours have arisen from the cells of the previously quiescent heterotopic tissue, or in which it composed the mass at the head of an intussusceptum have been reported.

During the last decade the steady increase in the use of subtotal resection of the stomach as surgical treatment for chronic gastric and duodenal ulcer, has brought up this subject of pancreatic rests from another angle, for it would appear that their presence in the pyloric region can produce radiological evi-

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²The authors wish to express their appreciation to Dr. G. Gavin Miller, Dr. C. J. Tidmarsh and Dr. F. G. Hicks for permission to use their cases in this report and to thank Dr. James G. Tye and Dr. W. S. Caveness for assistance rendered in collecting the material.

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dence and symptoms in many respects strikingly similar to those of ulcer, and lead to an operative procedure possibly more radical than the circumstances demand. In the routine pathological examination of approximately eight hundred stomachs over a period of six years, in our own experience this was the case in five instances and we have become interested in a further study of the subject from this standpoint. We have reviewed those cases reported in the literature which are relevant, and in conjunction with those in our own series attempted from all the information available to arrive at some conclusions that will be helpful in differential diagnosis. Discussion of the question as to the advisability of subtotal gastrectomy for pancreatic rests in the pyloric region is left to the surgeons and beyond the scope of this paper.

RELEVANT CASES IN THE LITERATURE

In 1909 Reynier and Masson (5) described the case of a 37 year old male who had suffered from stomach trouble for a long time. He had had attacks of bilious vomiting, becoming painful and more frequent and showed diminished acidity, both free and combined. Peptic ulcer and pyloric stenosis were considered and after medical treatment for sometime, the abdomen was opened. The pylorus was found to be free of adhesions, but a mass the size of a large pea could be palpated within it. Thinking it was an incipient carcinoma, the surgeon resected the pylorus and did a gastrojejunostomy. Considerable postoperative vomiting of bile occurred but this gradually disappeared without further surgical intervention. The mass was aberrant pancreatic tissue consisting of acini and islets and situated between the mucosa and muscular layer of the pyloric canal. It formed a polypoid protrusion into the orifice and was considered an adenoma, though it seems doubtful from the description and illustrations that it was actually neoplastic.

Gibson in 1912 (6) reported a pancreatic rest occurring in a woman, 25 years of age. She gave a history of epigastric pain, with occasional vomiting and tenderness in the right hypochondrium over a period of two years. The attacks suggested biliary colic. Exploratory laparotomy showed a circumscribed slightly elevated tumour the size of a 25 cent piece, an inch proximal to the pylorus on the anterior wall of the stomach. This was excised and the patient made a good surgical recovery. The lesion was reported erroneously by one pathologist as adenocarcinoma, but later found to be a pancreatic rest. Review of the X-ray plates, considered negative before operation, showed a thinner and shadowy appearance at the site of the mass. The author doubts if the anomalous condition was the cause of the symptoms as it did not impinge on the pyloric orifice and her symptoms later returned.

Reimann (7) presented before the Pathological Society of Philadelphia in 1919 the findings in a diabetic male, aged 56 years. The patient was operated

on for intense symptoms referable to the right hypochondrium. A mass was found in the right wall of the duodenum opposite the head of the pancreas. This was excised and found to be a pancreatic rest in the submucosa, over which lay an acute and chronic ulceration of the mucosa, 1 cm. in diameter and 0.3 cm. in depth. Ducts from the heterotopic tissue were disclosed by serial sections to open at the base of the ulcer. No islands of Langerhans were seen. The author did not feel justified in ascribing the presence of the ulcer to secretion of pancreatic juice, although ducts were demonstrated histologically; he felt that the ulcer may have been caused by the mere puckering of the mucosa from the fibrous tissue in the mass.

A case reported by Cohen (8) in 1922 concerns a man of 36 years who gave a five year history of gastric symptoms and medical treatment in three large hospitals. His complaints were quite typical of ulcer. The pains were associated with vomiting and occasionally his stools were "black as coal." He had slight tenderness and rigidity in the upper region of the abdomen and an indefinite mass was palpable in the epigastrium. The roentgenogram showed a persistent defect in the pyloric region, the duodenum was distended with the opaque meal and peristalsis was active. A residue remained on both sides of the pyloric sphincter six hours later. Gastric analysis showed high hydrochloric and total acidity. At operation a mass the size of a hickory nut was found in the pylorus, causing considerable narrowing of the lumen. A pylorectomy and posterior gastrojejunostomy were performed. The patient made an uneventful recovery without recurrence of symptoms. The mass on pathological examination was found to be 3 cm. in diameter and to involve both the pylorus and duodenum. It consisted of ducts and acini of pancreatic tissue supported by whorls of fibrous tissue. No true islands were seen. The ducts appeared to converge into a large duct which opened into an umbilicated elevation on the ulcerated surface.

Two of the six cases of pancreatic rests described by Delhougne (9) in 1924 concern us here. A 45 year old woman had suffered for months with indefinite pain in the upper abdomen which came on after meals. Her appetite was bad, but digestion regular. A tumour about the size of a walnut could be palpated in the pyloric region. X-ray showed nothing to support a diagnosis of carcinoma. Acid values were reduced. At operation a hard white appearing tumour as large as a three mark piece was found a thumb breadth from the pyloric orifice. This was resected with the pylorus. Sections showed the mucosa to be unchanged, but the submucosa and part of the musculature replaced by pancreatic tissue with islets and ducts. The patient made a complete recovery without return of symptoms. The second case is that of a 50 year old male who had had stomach trouble for four years and many operations. Finally a tumour the size of a nut was found in the pylorus. This

consisted of chronic inflammatory tissue and a pancreatic rest, containing both islets and ducts. The author calls attention to the fact that about half of all pancreatic rests in the stomach are submucous, while the other half are about equally divided between those involving the muscle, the serosa and more than one layer.

Choisser (10) in 1925 described the case of a 57 year old ex-service man who gave a history of pain in the epigastrium for a year and a half and considerable loss of weight. At the beginning the pain was intermittent, but later became continuous and at times acute, moreover it bore no relation to the taking of food or alkalies, but seemed to be exaggerated by the eating of meat. There was no nausea or vomiting and blood had not been noticed in the stools.

Physical examination showed the abdomen to be retracted and tense with tenderness throughout, but more marked above and to the right of the umbilicus. Fluoroscopic examination revealed the duodenal cap filled and smooth, the pylorus not freely movable, and no peristalsis at the lower end of the stomach, which showed no residue at the end of six hours. After a period of medical treatment, which was not successful, an exploratory operation was performed. This revealed the pylorus to be dilated and thickened, and to contain a tumour mass the size of an olive protruding into the lumen from the posterior wall. The mesenteric glands were enlarged and hard. As the lesion was considered cancerous and the patient's condition did not warrant pylorectomy, a gastroenterostomy was performed. He died three days later. Autopsy showed the mass to measure 1.5 x 2 cm. and to project into the lumen from beneath the mucosa. No ulceration had occurred. Two bile stained ducts were noted coming from the base of the mass and these appeared to anastomose and empty into one of the hepatic ducts. Histological examination disclosed the tissue to be pancreatic with ducts and islets. There was no evidence of malignancy.

A very extensive review of the subject of aberrant pancreatic tissue was made by Simpson (11) in 1927. He analysed 150 cases and mentions the fact that more than a score of these were operated upon because of clinical and roentgenological evidence of pyloric obstruction. In the cases which he reviewed 33 per cent showed the lesion to be located in the stomach and 17 per cent in the duodenum.

Attention to the aggravation of symptoms following the ingestion of meat in this condition was called first apparently by Cave (12) in 1928. He mentions the fact that physiologists state that meat causes more rapid secretion of pancreatic juice than either milk or bread and suggests that distention of the aberrant pancreatic tissue during its functional activity may be the explanation. His case concerns a woman of 64 on whom a cholecystectomy was performed and a mass of aberrant pancreatic tissue removed. The rest was

about 1 cm. in diameter and located in the wall of the duodenum distal to the pyloric vein, hence it is difficult to see how it could have had any obstructive effect upon the pyloric orifice.

The question of the possible rôle the pancreatic juice may play, in combination with other factors, in the production of peptic ulcers was raised by Wohlwill (13) in 1928 as the result of a case in which a duct leading from a pancreatic rest in the muscle of the stomach wall was found to empty into the base of a small gastric ulcer. The patient, a male of thirty, gave a history of ten years of medical treatment for the condition. Detailed clinical findings are not included, but it is noted that a slight subacidity of the gastric juice had been demonstrated.

In 1931 Tschudi (14) reported the case of a 42 year old woman who was sent to the hospital with a diagnosis of carcinoma of the pylorus. She had had a severe attack of vomiting three months before admission and since that time a persistent dragging sensation in the region of the stomach, which bore no relation to meals. Her appetite had failed completely and she had lost ten pounds in weight. Blood had not been observed in the stools. X-ray showed an obvious stenosis of the pylorus with deformed duodenal cap but only slight gastric delay. The acidity was reduced. At operation the stomach was found to be of normal size and shape except the pyloric ring was firm and had the shape of a signet ring, due to the presence of an intramural thickening on the side of the greater curvature. No scarring or inflammatory changes were demonstrable. As an incipient carcinoma was suspected resection was done. Gross and microscopic examination of the specimen revealed that the pyloric canal would admit the tip of the index finger and there was a pancreatic rest in the submucosa. This was sharply defined and about the size of a pea. The acini grouped themselves in grape-like fashion around medium sized ducts which broke through the muscularis and rolled up like a ball in the subserosa. No islands were seen and the mucosa was free. The patient made an uneventful recovery with gain in weight and no return of symptoms.

Four cases of aberrant pancreatic tissue in the wall of the stomach were described by King and MacCallum (4) in 1934. The patients were all males ranging in age from 37 to 72 years. One gave a two year history of indigestion. X-ray showed spasm of the proximal end of the pyloric antrum, not relieved by atropin. A nodule three quarters of an inch in diameter was found in the wall of the stomach, two and a half inches from the gastroduodenal junction. The second case also gave a history of indigestion for two years, with vomiting for the last four months. X-ray showed almost complete obstruction of the pylorus. This was resected and found to be made up of masses of epithelial cells, mostly of the type met with in Brunner's glands but containing a few pancreatic acini. A third case showed a small nodule of pancreatic tissue in

the lesser curvature, two thirds of the distance from the cardia to the pylorus. This patient died of nephritis and cardiovascular disease and never had any symptoms referable to the anomaly in the stomach. The last case had an ulcer in the lower part of the cardia. This was excised and histological sections showed several types of epithelial cells not normally present in this site and including pancreatic acini. The authors conclude on the basis of a study of these cases that contrary to the generally accepted view the pancreatic tissue arises from the epithelium of the stomach in adult life as the result of the action of abnormal stimuli.

The symptoms met with in the presence of pancreatic rests in the duodenum were thoroughly discussed by Best and Bowers (15) in 1934. They point out that peptic ulcer, cholecystitis and malignancy may be simulated, but the findings are not typical. There is mild pain in the right upper quadrant, often brought on by the eating of meat. Aversion to fatty food is noteworthy and poor gallbladder function is often found. Moreover a low gastric acidity is a helpful sign in contradistinction to peptic ulcer. Their two cases gave symptoms of biliary tract disease and were cured by removal of the lesion.

An excellent review of the whole subject of aberrant pancreatic tissue in the gastrointestinal tract was made by Branch and Gross (16) in 1935. Twenty-four cases with the patients ranging in age from 8 days to 82 years were described. In two of these the symptoms were gastric and directly referable to the anomaly. A woman of 65 gave a history of weakness and loss of weight of several years' duration. For the previous three months the appetite had been poor with vomiting after meals. Blood was present in the stools. She died five days later of bilateral lobar pneumonia. Autopsy revealed an aberrant mass of pancreatic tissue in the wall of the duodenum, 3 cms. distal to the pyloric ring. Over it the mucosa showed an indurated ulcer 1 cm. in diameter, supporting a fibrinous blood clot. Microscopical examination revealed the pancreatic tissue replaced completely the normal glandular structures and penetrated the entire duodenal wall. Acini and ducts were seen but no islet tissue. The bed of the ulcer rested in necrotic pancreatic tissue and chronicity was evident from the considerable fibrosis. The other case, a woman of 66, had suffered from sour eructations and indigestion for fifteen years. Epigastric pain coming on twenty minutes after meals occurred at times. Roentgen studies of the gastro-intestinal tract showed slight dilatation of the stomach with residue of from 40 to 50 per cent. There was a constant filling defect just proximal to the pylorus. The stomach wall however appeared flexible in this area. Gastric analysis showed free hydrochloric of 50 and total acidity of 70. At operation palpation of the stomach revealed a mass 1 cm. in diameter in the posterior wall in the prepyloric area. This projected into the lumen so as to partially obstruct the pylorus. The antral end of the stomach and part of the

pylorus were resected. The polyp was covered by mucous membrane and there was no peptic ulcer. The bulk of the tissue consisted of an anomalous mass of secretory glands and acini, partly of Brunner and partly of pancreatic type. Ducts from these emptied into the lumen of the stomach. No islets were observed.

Stohr and Kogler (17) in 1936 reported the case of a male of 34 years who complained of pain and loss of weight. X-ray showed a well formed but rather broad duodenal bulb. Duodenitis was diagnosed, and as he did not improve under medical treatment a laparotomy was performed. A tumour the size of the kernel of a hazel nut was found in the wall of the duodenum, about a finger breadth from the pylorus. It consisted of pancreatic tissue with ducts and islands. There was no ulcer. The patient made a rapid recovery without recurrence. The authors believe that the symptoms in such cases are due to spasm of the muscle which is brought about by activity of the aberrant tissue and inability of the secretion to get out. They stress the point that this diagnosis is to be considered in cases of gastric pain of several years standing coming on 3-4 hours after meals, where clinical and X-ray investigation gives uncertain or only suggestive evidence of ulcer.

A most extraordinary case was reported by May (18) in 1937. It concerns a woman of 28 who developed a cystic tumour mass in the abdomen over a period of two years. Her only symptom was amenorrhea, but she was found to have hyperglycaemia and a pancreatic cyst was suspected. At operation this was found to be thin walled, and seven liters of syrupy fluid were removed. The cyst was attached to the pylorus and at this point the mucosa was ulcerated. Pancreatic tissue was found at the junction of the cyst and stomach and in the wall opposite the point of attachment. There was no connection with the pancreas proper. The pancreatic tissue was believed to be of islet, not acinar type. The patient made an excellent recovery following excision and pyloroplasty. The author feels the ulcer in the stomach was due to trophic or mechanical, rather than digestive factors.

Whiteride's (19) case, reported in 1937, concerns a female of 22 who had suffered from bilious attacks for six years, and gnawing pain coming on soon after meals for two years. X-ray indicated an ulcer-appearing area in the first part of the duodenum. At operation a nodule 1 x 1.5 cm. was located at this site. This was found on microscopic examination to be a pancreatic rest. Excision gave complete relief of symptoms.

Of the two cases reported by Danzis (20) in 1938 one involved the pyloric region and concerns us here. A male, age 45 years, was admitted to the hospital for rectal bleeding. This had been noticed for 3 months with occasional tarry stools. No upper abdominal pain, nausea or vomiting had occurred. Gastrointestinal series showed "probable duodenal ulcer with some pyloric

retention." At operation the pylorus appeared hard and retracted near the duodenal junction. On the first portion of the duodenum a small nodular growth, firmly incorporated into the wall was found. A partial gastric resection was performed. On pathological examination the nodule was found to be 1 cm. in its circular diameter and 8 mm. thick. It involved all layers of the duodenum, and projected from the serosa. Acini, ducts and occasional islets were present. There was a considerable amount of inflammatory reaction but no chronic peptic ulceration. Leakage from the duodenal stump led to peritonitis and death ten days postoperative.

In 1940 Faust and Mudgett (3) reviewed the literature on this subject thoroughly, and made statistical studies of the distribution of 370 cases of aberrant pancreatic tissue in various parts of body, reported up to date. Their case was a male, 43 years of age, who entered the hospital complaining of diarrhea, abdominal pain, anorrhexia and weakness. X-ray showed a polyp located in the pyloric end of the stomach. There was no free hydrochloric and the basal metabolic rate was low. Subtotal gastrectomy gave only temporary relief, and the authors state that it is now evident that this polyp, which was composed of ducts and pancreatic acini, was not the cause of the symptoms.

Krieg (21) in an article appearing in 1941 stated that the majority of pancreatic rests are asymptomatic, and when not, are likely to be confused with ulcer and malignancy. He attributes the pain to interference with intestinal motility, local spasm, muscle hypertrophy, and contraction. He reported the case of a woman of 45 who suffered from periodic attacks of "gaseous indigestion" for 15 years. Certain foods provoked the attacks and soda gave relief. X-ray showed delayed gastric emptying. At operation a nodule of pancreatic tissue, 1.5 cm. in diameter was found in the pylorus. The stomach was dilated with hypertrophy of the wall. The ducts in the tissue did not appear to open on the surface and there was no ulcer.

Recently Brown, Flachs and Wassermann (22) have reported the case of a woman, aged 64 years, who was admitted to a hospital because of pain in the abdomen, loss of appetite, "sour stomach" and frequent vomiting. Except for some tenderness in the epigastrium upon deep pressure the physical examination was negative. X-ray revealed that in the right lateral position the ascending portion of the duodenum presented a contour deformity encroaching upon its lumen, apparently causing stenosis. This was found on operation to be due to a "tumour" which was resected. On microscopic examination this was thought to arise from aberrant pancreatic tissue, but no mention is made as to its benign or malignant nature.

PERSONAL OBSERVATIONS

In the examination of approximately eight hundred stomachs removed by subtotal gastrectomy in several hospitals over a period of six years we have

encountered aberrant pancreatic tissue as the only apparent pathological cause of the symptoms on five occasions. This is an incidence of 0.62 per cent. Four of these were located in or very near the pylorus and one in the second portion of the duodenum. In none of these cases was there evidence of peptic ulceration at the time of operation. Brief synopses from the various case histories follow.

Case 1. Mr. D. M. This 26 year old aircraft worker entered the Royal Victoria Hospital in the service of Dr. G. Gavin Miller on June 16, 1944, complaining of intermittent attacks of epigastric pain for the past six years. There was occasional nocturnal distress with definite food relief. "Hemorrhages from the stomach" occurred in 1941 and again in 1942. The patient's father is said to have suffered from stomach trouble, otherwise the family history and the past personal history are noncontributory. Physical examination was essentially negative. Gastric analysis showed a free HCl of 46 and a total acid of 58 at the end of one hour. X-ray examination of the upper alimentary tract on June 17, failed to reveal any abnormality.

On account of the persistent indigestion and the history of two hemorrhages, a subtotal gastrectomy was performed on June 22, 1944. No gross abnormality of the stomach or duodenum was determined at the time of surgery. The pathological report is as follows: "Specimen consists of 14 cm. of the distal end of stomach. On the posterior aspect of lesser curvature, 2.5 cm. proximal to the pyloric orifice is a mucosal variation 1.3 cm. in diameter. Numerous sections taken from the stomach fail to show any evidence of peptic ulcer. At the point described grossly, however, there is a heterotopic mass of pancreatic tissue. Most of this lies in the submucosa, but a small portion extends through the muscularis mucosa and into the lamina propria. It consists of small dark staining acini with rather irregular arrangement of the cells and no definite islands. Some small ducts, however, are seen." Anatomical summary: "Heterotopia of pancreatic tissue in mucosa and submucosa of stomach."

The patient made an immediate uneventful recovery and was discharged from hospital on June 30, the 9th day post-operative. He was readmitted to hospital two days later following a massive gastric hemorrhage, the origin of which was considered to be the anastomotic site. The hemogram showed a red blood cell count of 1,730,000 with 34 per cent hemoglobin (5.3 gm./100 cc.), after initial emergency transfusion of 900 cc. of whole blood. He continued to bleed, and repeated transfusions were necessary up to July 12th. He was finally discharged from hospital on August 8, 1944, at which time his hemoglobin had risen to 63 per cent and there had been no bleeding for four weeks. Fifteen months later he was reported to be doing active farm work and having no trouble with his stomach.

A review of the films on this case reveals no deformity of the pyloric antrum nor of the duodenal cap. The gastric rugae are somewhat thickened throughout. There was nothing in the roentgenographic examination to confirm the strong clinical suspicion of peptic ulcer.

The haemorrhages from the stomach three and two years prior to operation in this case cannot be explained completely by the pathological examination of the

surgical specimen. It is possible that the pancreatic tissue may have led to acute ulceration and bleeding. There was no evidence of a healed peptic ulcer with scarring, nor does it seem likely that the nodule in the wall of the pylorus caused any appreciable gastric delay.

Case 2. Mr. E. R. This 40 year old office worker was admitted to the Royal Victoria Hospital in the service of Dr. C. J. Tidmarch on March 5, 1940. Indefinite epigastric distress had been present for the past eight years. This was described as "an empty feeling," but there was definite food relief. Three months prior to admission he had had a severe hematemesis, but there had been no further bleeding from the gastro-intestinal tract since that time. The family and past personal history were not relevant, and physical examination was essentially negative. Roentgenological examination of the upper alimentary tract showed no apparent abnormality of the oesophagus or stomach, other than slightly thickened gastric rugae. No definite niche could be seen in the pyloric region, but the rugae appeared to be drawn to a point on the lesser curvature just at the pylorus, suggesting healed ulcer. The duodenal cap and loop showed no apparent deformity.

On account of the massive hemorrhage, his age and long history of indigestion, it was decided to operate and he was transferred to surgery. A subtotal gastrectomy was performed by Dr. G. Gavin Miller. The operative notes state that the duodenum was divided just distal to the pylorus, and about three fourths of the stomach were resected. No ulcer was demonstrated at the time of surgery. The pathological report is as follows: "Specimen consists of a tubular portion of the pyloric end of the stomach, measuring 12 cm. in length. Except for slight congestion of the mucous membrane, the appearance of the specimen is not remarkable. No evidence of ulcer could be found grossly. A large number of sections were taken from the specimen. They show no evidence of inflammation or ulceration of the mucosa. There is, however, a heterotopic nodule of pancreatic tissue in the submucosa of the pyloric region. This tissue contains acini of parenchyma and small ducts, but nothing that could be positively identified as island tissue." Anatomical diagnosis: "Heterotopia of pancreatic tissue in submucosa of pylorus." The patient had a normal post-operative course and was discharged from hospital on March 20, 12th day post-operative. A six months, and also one year follow-up revealed that the patient had had no return of his digestive complaints.

A review of the films on this case fails to reveal any gross deformity of the contour of the duodenal cap. There is, however, some apparent mucosal irregularity in the region of the pylorus. This was apparently, considerably more prominent at the time of fluoroscopy.

As in Case 1 no satisfactory explanation of the haemorrhage three months prior to operation was found in the surgical specimen. Review of the histological sections showed the heterotopic pancreatic tissue, which had not been noticed in the gross examination to be situated at the pyloric orifice. For the most part it occupies the submucosa, but beneath it the circular muscle layer is here and there absent, leaving merely the thin outer longitudinal layer, and at one point this is reduced to only a

few strands of fibres (fig. 1). This anomalous arrangement and deficiency of the muscular layers are a strong argument for the purely developmental nature of the lesion and it seems very probable that in this case there may have been some disturbance in the functional activity of the pylorus.

Case 3. Mr. J. T. G. A. This 24 year old airforce mechanic was first admitted to Ste. Annes Military Hospital on January 16, 1945. He gave a long history of indigestion characterized by nausea with epigastric and lower abdominal pain. The pain awakened him at night and there was food relief. An appendectomy was per-



FIG. 1. CASE 2. LOW POWER MAGNIFICATION OF SECTION THROUGH MASS OF HETEROTOPIC PANCREATIC TISSUE IN THE WALL OF THE PYLORUS

Note the mucous membrane is elevated slightly by the mass which is here confined to the sub-mucosa. Beneath it the thick circular muscle layer is wanting, while the fibers of the longitudinal coat are present. The deficiency in the mucous membrane is an artifact.

formed on January 24th. Exploration of the abdomen at the time of the appendectomy failed to disclose evidence of abnormality in the upper alimentary tract. A retrocaecal appendix, 10 cm. long, was surrounded by thick adhesions and contained numerous fecoliths. The terminal ileum appeared normal, although there were enlarged glands in the mesentery. No acute inflammatory change, though some evidence of chronic inflammation was seen in the sections of the appendix on pathological examination.

Preoperative roentgenological investigation had demonstrated spasm and irregularity of the apex of the duodenal cap. No apparent ulcer crater was present. There was some evidence of gastritis (figs. 2 and 4A).

On patient's readmission to hospital on August 17, 1945, he said there had been no change in his digestive complaints. A gastric analysis showed a free HCl of 26 and total acid of 42 at the end of one hour. After histamine the free HCl was increased to 55 and the total acid to 80 degrees. Roentgenological investigation of the upper alimentary tract again revealed apparent spasm and possible scarring of the apex of the duodenal cap, (figs. 3 and 4B). There was no suggestion of an active ulcer crater. Patient showed no subjective improvement under medical regime and an exploratory laparotomy was deemed indicated by Dr. F. G. Hicks, surgical consultant. His report is in part, as follows: "...The stomach walls felt thickened, as



FIG. 2. CASE 3. APPEARANCE OF STOMACH AND DUODENUM ON FIRST ADMISSION IN JANUARY 1945. SOME EVIDENCE OF GASTRITIS, NARROWING OF APEX OF DUODENAL CAP

though a certain amount of gastritis was present. ...No definite signs of gastric or duodenal ulceration were present, but on palpation of the pyloric region, a definite small tumefaction, which was independent of the pyloric muscle, was evident." A subtotal gastrectomy was performed.

The report of the pathologist stated: "Specimen consists of the distal end of the stomach, including the pyloric ring and 1.5 cms. of the first portion of the duodenum. There is no evidence of ulceration in the gross specimen, but the pylorus appears thickened at one point. Sections show an area on the lip of the pylorus, at a point where the mucosa is transformed to duodenal type, in which the submucosa is



FIG 3 CASE 3 APPEARANCE OF STOMACH AND DUODENUM ON RE-ADMISSION IN AUGUST 1945 PERSISTENT NARROWING OF APEX OF CAP



FIG 4 CASE 3 1—SPOT FILM OF CAP IN JANUARY 1945
B—SPOT FILM OF CAP IN AUGUST 1945

There is narrowing of the apex of the cap, but no apparent mucosal disturbance in pylorus

thickened and replaced by pancreatic tissue This consists of lobules containing acini and ducts but no islets are identified. The heterotopic tissue is beneath the

muscularis mucosa and extends down into the muscular coat splitting the fibers. There are no inflammatory changes. Diagnosis: Heterotopia of pancreatic tissue in lip of pylorus."

Gastric analysis on the 24th postoperative day showed no free HCl and a total acidity of 5 degrees. Recovery was uneventful and the patient was discharged from hospital on the 26th day. As yet no follow up report has been obtained.

A review of the films on the case fails to reveal evidence of deformity of the pylorus. The irregularity and narrowing of the apex of the duodenal cap is well shown on the "spot films," made in January, and again in August 1945. (See fig. 4.) Both these examinations were performed by one of us (E. W. H.) The cap shows no appreciable deformity of its base, nor is there evidence of pyloric irregularity. No explanation for the contracted apex was afforded by the surgeon or pathologist.

In this case the location of the pancreatic rest is such that it may well have led to interference with proper emptying of the stomach.

Case 4. Mr. A. B. This 43 year old patient was admitted to Ste. Annes Military Hospital on November 20, 1943. His chief complaint on admission was intermittent epigastric distress, not particularly related to food intake. The patient was a chronic alcoholic, and it was felt that his history was not reliable. There was occasional nocturnal pain, but he denied food relief. Roentgenological examination of the upper alimentary tract on December 3, 1943 demonstrated no gross abnormality of the oesophagus or stomach. The duodenal cap was small, spastic and irritable and did not fill out well at any time during the examination. There was considerable mucosal irregularity in the cap with questionable focal deformity in its central portion. The radiologist requested an opportunity to re-examine the patient following a course of medical regime in the hope that a more satisfactory visualization of the cap could be obtained. No further radiological examination was made, however.

A laparotomy was performed on December 8, 1943 by Dr. F. G. Hicks. Numerous adhesions were found fixing the pylorus and first portion of the duodenum to the posterior abdominal wall. An indurated area on the anterolateral aspect of the first part of the duodenum was considered to represent an ulcer. The duodenum was cut across by cautery below this lesion and a subtotal gastrectomy performed. The pathologist could find no evidence of ulceration in the specimen submitted. The indurated area discovered by the surgeon measured 0.8 cm. in diameter and was lying in the muscular wall and submucosa, 0.7 cm. beyond the pylorus. The overlying mucosa was intact. Sections through this area disclosed adult pancreatic tissue with a few clear islet cells and several ducts. Anatomical diagnosis: "Pancreatic rest of duodenum."

Patient made an uneventful recovery and was discharged from hospital on January 12, 1944. No follow up report could be obtained.

The roengenoscopic examination on this case was carried out by one of us (E. W. H.) and on reviewing the films, there is no apparent focal deformity of the cap that could be considered to represent the pancreatic rest, as described by the pathologist. The cap is incompletely shown on the films.

The heterotopic pancreatic tissue in this case was noted by the surgeon and thought possibly to be the indurated tissue of a peptic duodenal ulcer. Review of the slides shows no evidence of inflammatory reaction or ulceration. In this location 0.7 cm. beyond the pylorus, it would seem that it would more likely cause symptoms through secretory activity.

Case 5. Mr. R. L. This 41 year old patient was referred by Dr. C. J. Tidmarsh to the service of Dr. G. Gavin Miller at the Royal Victoria Hospital on October 4, 1941. The complaints on admission were gastric distress and fullness after meals for the past three years. The pain radiated to the back and was relieved by taking milk. There was no vomiting, hematemesis or melena. The roengenological examination of the upper alimentary tract demonstrated tortuous gastric rugae and hyperactive peristalsis. The base of the duodenal cap presented some minimal deformity and irregularity, suggesting possible superficial ulceration, but there was a considerable degree of spasticity and irritability of the cap generally. Gastric analysis showed a free HCl of 40 and a total acid of 54 at the end of one hour.

A subtotal gastrectomy was performed on October 7th. No ulcer crater could be demonstrated in the stomach or the first portion of the duodenum by the surgeon. There was marked induration of the head of the pancreas, possibly secondary to old ulceration of the second portion of the duodenum. A small white plaque was noted on the anterior wall of the second portion of the duodenum and this was removed. The following report was received from the pathologist on the surgical material "Specimen A consists of a stomach including 15 cm. of the greater and lesser curvatures and pylorus sewn in the form of a pouch. The serosal surface is smooth and glistening. On section the wall does not appear appreciably thickened. There are several areas of haemorrhage scattered throughout the mucosa but no evidence of ulceration. Specimen B consists of a mass of reddish white tissue measuring 5 x 1 x 0.5 cm. It shows no gross evidence of ulceration. Histological sections prepared from the stomach show some oedema of the submucosa with dilatation and congestion of the vascular channels. Sections taken through the duodenal tissue show the presence of pancreatic tissue. This for the most part is located in the submucosa with slight extension into the muscular layers. It consists of irregularly arranged ducts and acini. No islets are identified. There is no evidence of ulceration. Diagnosis: Heterotopic pancreatic tissue in duodenum." The postoperative course was uneventful and the patient was discharged on the 13th day. Four years later he reported that he had had no return of the gastric symptoms, felt very well, and was able to eat and drink quite normally.

A review of the films on this case fails to reveal any abnormality of the second portion of the duodenum. The cap itself, appears spastic, as was reported by the fluoroscopist.

The pancreatic rest in this case was quite small and on histological examination consisted mostly of irregularly arranged ducts with comparatively little parenchyma. It seems doubtful from its size and structure that it could have had any appreciable functional activity, moreover its distance from the pylorus excludes the possibility of any mechanical interference with emptying of the stomach.

DISCUSSION

From the considerable number of cases reported in the literature, the more important of which have been synopsized above and the five in our own series, several points concerning these pancreatic rests in the pyloric region arise for discussion.

The incidence of heterotopic pancreatic tissue in this area is not as yet clearly established. Taking the whole gastrointestinal tract, Letulle (23) has reported its occurrence on six occasions in 2,000 autopsies, and Opie (24) ten times in 1800 post mortem examinations. Higher figures however are given by Katsurada (25) with six in 329, and Feyrter (26) with twenty-one out of 1,100 individuals. In 1,970 consecutive autopsies performed in the department of pathology of McGill University, Duff, Foster and Bryan (27) found twenty-one instances of the anomaly. If we combine these statistics it would appear that the incidence of a pancreatic rest in some part of the body is 0.9 or approximately 1 per cent. Sobotta (28) has raised the question of the possibility of considerable racial differences in this respect. Faust and Mudgett (3) in a summary of 370 cases reported in the literature to 1940 showed about 50 per cent to be located in the stomach and duodenum but no figures are given for the pyloric area alone. In Feyrter's (26) series four out of twenty-one were in the pars pylorica. From these figures we might conjecture that about a quarter of all cases occur in this region or that they are met with in this site in 0.25 per cent of the population. In four of the five cases here reported, the aberrant tissue would be considered at the pylorus and the incidence therefore in the 800 cases is two times that of people as a whole. The series is not sufficiently large to be sure that this increase is significant, but it tends to support the view that heterotopic pancreatic tissue in the pyloric region can, indirectly at least, produce symptoms.

While all five cases of our own series are males, many examples of the condition have been reported in females. As a whole, however, there does appear to be an increased incidence in men over women of about two to one. As regards age, the cases that have come to operation are almost entirely adults well distributed through the decades from the twenties to the sixties. This fact is felt by some to argue against the developmental character of the lesion. However examples are met with in infants operated upon for hypertrophic stenosis and the histological appearance of these rests is certainly in favour of their congenital nature.

The symptomatology of these cases is strikingly similar, but not pathognomonic. Often there is a rather long history of indefinite pain in the abdomen with a slight tenderness in the epigastrium. This gradually gets worse as time goes on and may be accentuated by the eating of meat. It may or may not be relieved by food or alkalies. Loss of appetite, sour eructations, nausea

and even vomiting are likely to develop and bring the patient to the physician. Haemorrhage with either haematemesis or the passing of blood in the stools has occurred in several cases. The acidity of the stomach varies. It may be normal, even high, but frequently is appreciably reduced. Only in the case described by Faust and Mudgett is achlorhydria reported. The picture is suggestive of peptic ulcer, cholecystitis or malignancy, but as many authors have pointed out the findings do not fit clearly into any one of these diagnoses.

The equivocal character of the X-ray findings is also noteworthy. It should be borne in mind that the ulcer symptom complex may be present in the absence of roentgenological and pathological evidence of peptic ulceration in the stomach or duodenum. In two of five cases presented, there was also a history of haemorrhage from the upper alimentary tract. The surgical specimens showed no ulceration but revealed pancreatic rests, which in four cases (Cases II, III, IV, V) apparently were responsible for causing some roentgenological abnormality. Though such inclusions of heterotopic pancreatic tissue in either the pre- or post-pyloric region, may cause a deformity of the barium silhouette, it does not seem likely that the resultant mucosal defect could simulate ulceration as exemplified by barium retention in an ulcer niche (29). A possible exception to this, according to the literature, is when the arrest produces a diverticulum, or a duct opening is sufficiently large to retain barium. Neither of these conditions were observed in any of our cases. On the other hand, apparently adjacent spasm may cause focal deformity in the nature of an incisura to suggest ulceration as in Cases II and IV (4, 14). In none of the cases, however, was an absolute and positive radiological diagnosis of ulcer formulated. In Case I the arrest appeared to be sufficiently proximal to the pylorus so that there was no associated functional disturbance of the duodenal cap. Strong clinical history, substantiated by certain roentgenological variations from normal, may influence the surgeon to a considerable degree, even in the absence of positive demonstration of an ulcer crater. Thus irritability and spasm of the duodenal cap, together with some minor deformity in the region of the pyloric orifice, may be findings of exaggerated diagnostic significance as presumptive or confirmatory evidence of peptic ulceration. The failure of a juxta-pyloric lesion, as seen roentgenologically, to respond to medical management must suggest the possibility of a pancreatic rest in the differential diagnosis.

There is no doubt that pancreatic rests can remain asymptomatic and one hesitates to be dogmatic as to the primary rôle that the lesion plays in many of these cases. If we accept the view that they are congenital, the fact that these individuals, apparently, in the vast majority of cases, have no digestive disturbance and do not come to operation until adult life is reached, has yet to be explained. There must be at least other contributing factors. From the

cases reviewed above, however, it is obvious that heterotopic pancreatic tissue in the region of the pylorus can produce serious consequences in several different ways. First and probably most important of these is actual interference with the passage of the stomach contents through the pyloric canal when the mass protrudes as a polypoid excrescence into the lumen. This is well exemplified in cases described by Reynier and Masson (5), Choisser (10), King and MacCallum (4) and Branch and Gross (16). Second though there may be no actual stenosis, the presence of this tissue in the muscular wall can in all probability interfere with its peristaltic activity. Our cases 2 and 3 and those of Delhougne and of Tschudi appear to fit into this group. Third there are those where a peptic ulcer has arisen apparently from the discharge of pancreatic juice through a duct into its base. No ulcers were found in our series but they were met with by Reimann (7), Cohen (8), Wohlwill (13) and Branch and Gross (16). Four even though an ulcer is not present, the possibility that the activity of the tissue or its excretion may cause functional disturbance has been raised by Cave (12), Best and Bowers (15), Stohr and Kogler (17) and would have to be considered in our fourth case. Finally that benign and malignant neoplasms may arise from such aberrant tissue is well recognized and was believed by May (18) and by Brown, Flachs and Wassermann (22) to have occurred in their patients. It would appear, therefore, that each case must be studied carefully by the pathologist to determine so far as possible to what extent the above factors play a rôle in the pathogenesis. In some the answer seems quite obvious, but in others it may well be, the presence of the pancreatic rest is purely coincidental.

SUMMARY

Five cases are reported from a series of approximately eight hundred stomachs examined following subtotal gastrectomies, in which a pancreatic rest in the region of the pyloric orifice was the only pathological lesion found to account for the symptoms.

The incidence of the anomaly in this series would appear to be higher than that met with in the population as a whole.

A review of the literature and our own cases indicates that this condition may cause gastric disturbance in several different ways.

No pathognomonic symptomatology or radiological picture could be established, but this disease should be borne in mind in cases suspected of having peptic ulcer, malignancy or cholecystitis when the findings are not typical.

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THE EFFECT OF TWO NEW HISTAMINE ANTAGONISTS (BENADRYL AND COMPOUND 63) ON HISTAMINE STIMULATED GASTRIC SECRETION IN THE DOG

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INTRODUCTION

Therapeutically it would be very desirable to possess a pure chemical substance which could be used to abolish the secretion of gastric juice without causing objectionable side reactions. Enterogastrone or urogastrone possesses such promise, but they have not been isolated or sufficiently concentrated for general use. In the meantime, it may prove to be profitable to attempt to find a potent inhibitor of gastric secretion among the new group of compounds referred to as "histamine antagonists."

This report deals with a study of two recently synthesized histamine antagonists in regard to their ability to counteract the secretory excitatory effect of histamine on the gastric glands. The substances studied are "benadryl" (1) (β -dimethylaminoethyl benzhydryl ether hydrochloride) and "compound 63" of Mayer and associates (2) (N' pyridyl- N' benzyl- N /dimethylethylenediamine).

Previous studies on the ability of histamine antagonists to inhibit histamine stimulated gastric secretion have failed to reveal a significant antagonism in the case of the Fourneau compound 929F (3) and only small effects in the case of other synthetic histamine antagonists (4). The Fourneau compound 1571F was found to cause a moderate inhibition of the gastric secretion provoked by 0.5 mg. of histamine in Heidenhain dogs (5) but no diminution of the response occurred when doses of histamine several times that large were used (6).

One of the compounds used in the present study, benadryl, has been tested for its effectiveness in counteracting the histamine stimulus to gastric secretion. Loew (7), using the double histamine test in Heidenhain pouch dogs found that three out of four dogs showed an average decrease of 40 per cent in the amount of acid secreted in response to histamine when benadryl in a dose of 10 mg./kg. was administered subcutaneously. In persons receiving histamine by slow intravenous infusion the simultaneous administration of benadryl intravenously produced a moderate depression of the gastric acid secretion in four out of seven cases (8).

METHODS

Four mongrel dogs with pouches of the entire stomach and esophago-duodenostomies were used. The assay procedure was that of Ivy and Gray (9).

Histamine was given subcutaneously every ten minutes (0.025 mg. of histamine dihydrochloride¹ in 0.5 ml. of water). The gastric juice was collected every twenty minutes; collection of gastric juice was not started until about 6 doses of histamine had been given by which time the rate of flow had become relatively constant. When three control samples had been collected, the drug to be tested was administered by subcutaneous injection in a dose of 50 mg. and the periodic collection of gastric juice was continued for 80 minutes. The volume of each sample was measured and the free acid concentration estimated by titration with N/40 HCl using p-dimethylaminoazobenzene as indicator. The

TABLE 1

DOG NO.	NO. OF TESTS	VOLUME (cc.)								OUTPUT OF FREE HCl (MG.)							
		Minutes before test compound			Minutes after test compound					Minutes before test compound				Minutes after test compound			
		60	40	20	20	40	60	80	60	40	20	20	40	60	80		
Compound # 63																	
1	3	7.8	5.0	4.4	6.0	4.1	4.7	6.1	7.7	7.1	6.5	6.2	2.8	5.2	5.2		
2	3	8.2	6.1	7.9	6.2	3.8	4.5	6.8	32.7	27.5	36.8	22.7	12.1	14.9	27.6		
3	3	7.4	11.2	10.9	10.7	12.7	14.7	13.5	32.2	39.8	38.8	36.0	42.7	35.5	39.5		
4	3	13.4	11.6	15.8	17.9	18.1	12.3	12.4	55.3	50.8	71.6	68.8	64.9	51.6	56.0		
Average.....		9.2	8.5	9.4	10.2	9.7	9.0	9.7	31.9	31.3	38.4	33.4	30.6	26.8	32.1		
Benadryl																	
1	3	6.5	7.8	8.3	6.6	6.9	6.3	7.8	11.5	15.6	20.9	17.0	17.3	9.8	14.4		
2	3	8.7	9.1	7.5	6.8	6.8	7.4	7.3	30.8	39.4	31.6	27.7	28.5	28.3	27.8		
3	3	13.5	13.7	13.9	19.5	16.5	15.2	17.3	51.5	56.1	50.1	87.6	64.5	57.8	69.0		
4	3	12.0	13.5	14.5	12.2	20.8	14.8	18.4	49.5	63.2	66.1	53.1	98.2	64.9	79.3		
Average.....		10.2	11.0	11.0	11.3	12.7	10.9	12.7	35.8	43.6	42.2	46.3	52.1	40.2	47.6		

dogs weighed between 10 and 12 kilograms each so that the dose of drug on the basis of body weight was 4.5 to 5.0 mg. per kilogram.

RESULTS

The results are presented in tabular form (table 1).

DISCUSSION

The average volume of secretion and output of free acid were not reduced significantly by either drug. A tendency toward reduced secretion after injection of the test compounds is shown by dogs No. 1 and No. 2; however, the

¹ Imido, Roche.

average for all tests on all dogs shows no significant alteration. The moderate inhibition of secretion observed by Loew (7) using a dose of benadryl twice as large as that used in the present study was not considered by him to be due to a specific antagonism between benadryl and histamine in regard to gastric secretion because of the inconsistency of his results and because the degree of inhibition was not nearly so great as that obtained when the effect of benadryl on other physiological actions of histamine were studied (e.g., contraction of isolated intestinal muscle and vasodepressor action). Lowe concluded that, since these compounds probably exert their effect by blocking entry of the stimulatory drug on to the receptor mechanism of the effector cell (analogous to the atropine-acetylcholine antagonism), benadryl probably has less affinity for the gastric gland cells than for other cells activated by histamine. This hypothesis appears to be substantiated by the results of the present work.

SUMMARY AND CONCLUSIONS

The synthetic histamine antagonists β -dimethylaminoethyl benzhydryl ether hydrochloride and N'pyridyl-N'benzyl-N/dimethylethylenediamine in doses of 50 mg. per kilogram subcutaneously do not reduce significantly the response of the gastric glands of dogs to stimulation by histamine administered subcutaneously every ten minutes.

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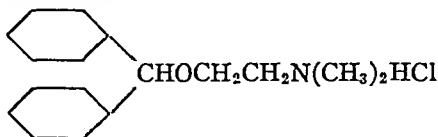
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THE INFLUENCE OF BENADRYL (DIMETHYLAMINOETHYL-BENZHYDRYL ETHER HYDROCHLORIDE) ON GASTRIC ACIDITY¹

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INTRODUCTION

Dimethylaminoethylbenzhydryl ether hydrochloride with structural formula as noted below, has been shown to possess marked anti-spasmodic and anti-histamine properties (1, 2, 3, 4).



The current conception that histamine normally has an important rôle to play in the production of hydrochloric acid by the stomach (5, 6, 7) has led to a study of the influence of this benzhydryl alkamine ether upon the gastric acidity of 8 normal subjects and upon that of 5 patients with a gastro-intestinal neurosis.

METHODS

In all of the subjects, the initial values for free and total acid were within the normal range. Two hundred, 300 and 400 mg. of drug have been administered daily in divided doses for periods of from two to seven weeks on any given level of dosage.²

Gastric acidity has been determined in each subject before and at 15 minute intervals following the administration of 50 cc. of a 7 per cent alcohol meal. All values have been expressed as the number of cubic centimeters of decinormal sodium hydroxide solution which would be necessary to neutralize 100 cc. of gastric juice, each cubic centimeter representing 1 degree of acidity.

RESULTS

The averaged results are shown graphically in figures 1, 2, 3, and 4. The earliest effect upon gastric acidity was observed in one of the control subjects who had received 200 mg. of the drug daily for 11 days. In that instance, the fasting free acid value dropped from 58 to 0 degrees and the total fasting acid figure from 77 to 8 degrees. After the alcohol meal, the first specimen also

¹ From the New York Medical College, Metropolitan Hospital Research Unit, Welfare Island, New York City.

² Generous supplies of this material under the name of "Benadryl" have been made available through the courtesy of Dr. E. A. Sharp, of Parke, Davis & Co., Detroit, Mich.

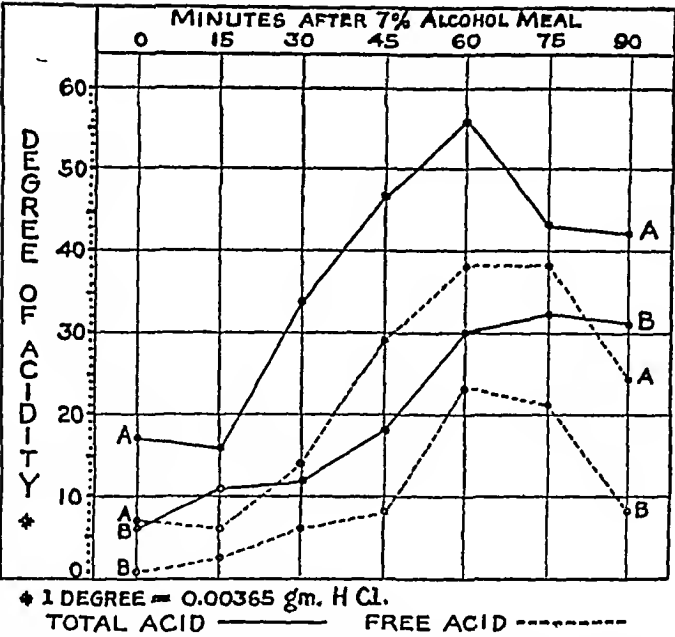


FIG. 1. AVERAGED DATA FOR THE FRACTIONAL GASTRIC ANALYSES OF THREE NORMAL SUBJECTS BEFORE (A) AND AFTER (B) RECEIVING DI-METHYL-AMINO-ETHYL-BENZHYDRYL-ETHER-HYDROCHLORIDE—200 MG. DAILY FOR 2.3 WEEKS

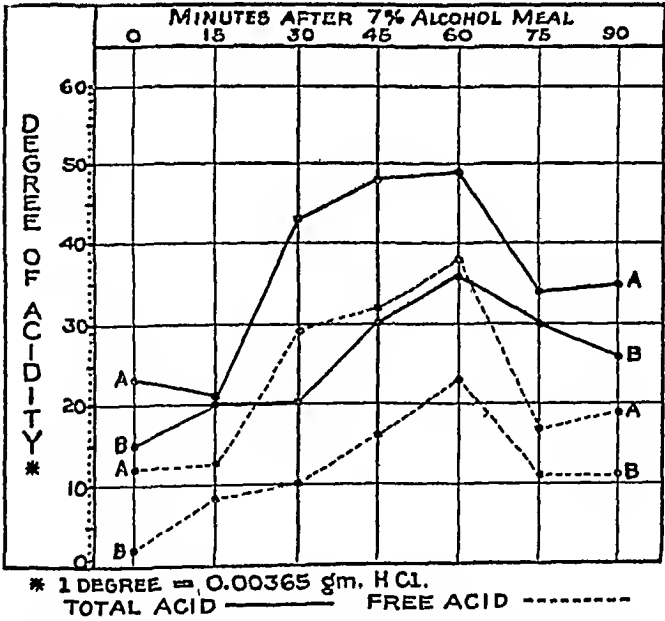


FIG. 2. AVERAGED DATA FOR THE FRACTIONAL GASTRIC ANALYSES OF THREE NORMAL SUBJECTS BEFORE (A) AND AFTER (B) RECEIVING DI-METHYL-AMINO-ETHYL-BENZHYDRYL-ETHER-HYDROCHLORIDE—300 MG. DAILY FOR 3.0 WEEKS

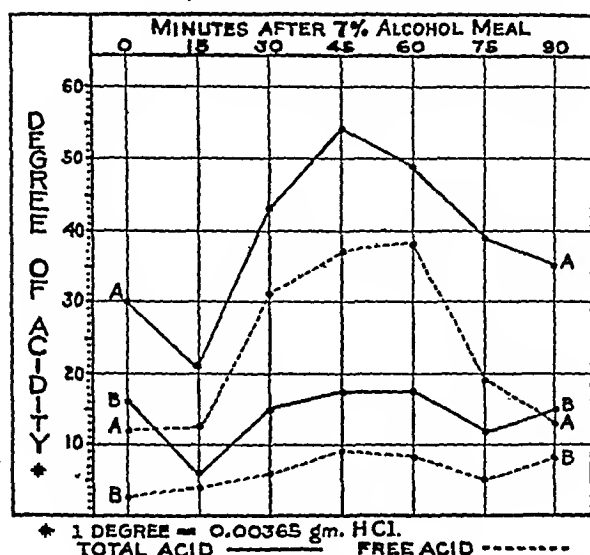


FIG. 3. AVERAGED DATA FOR THE FRACTIONAL GASTRIC ANALYSES OF TWO NORMAL SUBJECTS BEFORE (A) AND AFTER (B) RECEIVING DI-METHYL-AMINO-ETHYL-BENZHYDRYL-ETHER-HYDROCHLORIDE—400 MG. DAILY FOR 3.5 WEEKS

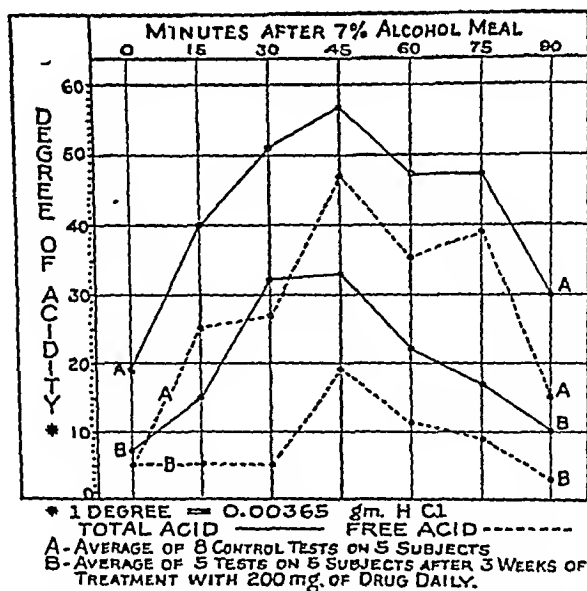


FIG. 4. VARIATIONS IN GASTRIC ACIDITY PRODUCED BY DI-METHYL-AMINO-ETHYL-BENZHYDRYL-ETHER-HYDROCHLORIDE IN FIVE PATIENTS WITH GASTRO INTESTINAL NEUROSES

showed a decrease in both the total and free acid, but values for subsequent specimens were similar to those observed in the control analysis. Another healthy subject showed normal acidity throughout both of his control tests. However, following a three weeks period of treatment with 300 mg. of drug daily, there was a complete absence of free acid and the total acid did not exceed twelve degrees in any specimen. After a further period of two weeks during which 400 mg. of drug were taken daily, free acid was still absent and the total acid did not rise above 5 degrees in any specimen.

In all subjects the acid values returned to their previous levels at variable intervals after the drug was stopped. As a rule the actual time required in any individual instance was directly proportional to the size of the dose and the period of time over which used. Even after the largest doses of 400 mg. daily for periods up to 7 weeks, the gastric acidity routinely returned to normal within three weeks, and the average time for such a reversion was about 10 days.

Despite the marked changes in gastric acidity, none of the normal subjects complained of any gastro-intestinal symptoms. In those subjects who were suffering from gastro-intestinal symptoms of a functional type, the drug usually afforded some relief. This was particularly true of the pains experienced by the 3 patients who had a spastic colon. It was equally true of the nausea of two others with less well defined complaints. That these responses were not psychic was proven by the use of an identically appearing placebo prior to the giving of the drug. The clinical effects of the drug in a larger series of cases are fully detailed elsewhere (8).

CONCLUSION

It is concluded that dimethylaminoethylbenzhydryl ether hydrochloride has a depressant effect upon gastric acidity when administered orally in any therapeutic range of dosage. A similar effect has been reported during the slow continuous intravenous injection of the drug (9). These observations indicate the anti-histamine nature of the action of the drug, and appear to be sufficient to warrant extensive trial in the management of peptic ulcer.

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SECONDARY PELLAGRA CAUSED BY MULTIPLE ARGENTAFFIN CARCINOMA OF THE ILEUM AND JEJUNUM

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INTRODUCTION

It is now generally believed (1, 2) that pellagra as a clinical syndrome is related to a deficiency, or to a lack of absorption of, or to an unsupplied increased demand for certain food factors, particularly certain of the B-complex vitamins, phosphorus and protein. Of the vitamins, a deficiency of nicotinic acid, riboflavin and thiamin are considered to be of greatest importance. However, Gillman and Gillman (3) of South Africa, found that in infantile pellagra among the natives, where severe forms of malnutrition are frequently seen, the addition of these vitamins invariably made the patients worse and increased the fatty changes in the liver cells, as determined by repeated liver biopsies. They found, on the other hand, that dried stomach (ventriculin) therapy plus hydrochloric acid caused rapid improvement and a rapid removal of the fat from the liver. As the stools from these patients were reported as being fatty one would wonder if an association with sprue did not exist.

Pellagra is usually classified as related to three groups of causes. The endemic form, so frequently seen among the poor people of the South, is clearly associated with their inadequate diets. The same may also be caused by voluntary inanition and the use of unbalanced faddist diets. Among chronic alcoholics a reduced intake of vitamin-rich foods and their substitution by the carbohydrate value of the alcohol may lead to the same condition, either with or without neuritis; and thirdly, pellagra may occur as an episode secondary to a great many varied causes which interfere with the orderly processes of the individual's nutrition.

In the exhaustive report of Bean, Spies and Blankenhorn (1) 388 patients with secondary pellagra were studied. In the larger number of these cases the pellagra was associated with diseases of the gastrointestinal tract. Many diverse lesions were recognized as causative agents in their series of cases. Infections and neoplasms of the mouth and throat, lesions causing partial obstruction of the esophagus, stomach, duodenum, ileum, colon and rectum were common causes. Carcinoma of the stomach, peptic ulcer, regional ileitis, ulcerative colitis, tuberculous enteritis, bacillary dysentery and parasitic diseases frequently underlay the impaired nutritional status of the patient. Cirrhosis of the liver was present in 17 cases, gallbladder disease in four. One instance of primary hepatoma engrafted on associated cirrhosis was noted, but extensive metastasis within the liver seemingly played a minor rôle. The

appendix and the jejunum were rarely involved with pellagrous symptoms, unless following an operation partial obstruction resulted.

The following case was deemed worthy of reporting because a careful search through the literature available to us has failed to reveal another instance of pellagra secondary to argentaffinoma of the ileum. Carcinoid¹ tumors of the gastrointestinal tract have been reported with increasing frequency in the past few years. Ritchie and Stafford (4) in September, 1944, reported 11 cases from the Wisconsin General Hospital, which added to those previously reported totalled 332 up to this time. All portions of the gastrointestinal tract have been found to be the primary site of the tumor, although the terminal ileum and the appendix have been involved most frequently. Lemmer (5) in 1942, reported the case of a 44 year old woman who underwent gastric resection for bleeding gastric ulcer and at operation a carcinoid tumor 1 cm. in diameter was found in the cardia, and adjacent to it a metastatic mass 7 x 6 x 5 cm. in size which was similar histologically to the primary nodule. Basse (6) reported in 1943 a case of carcinoid tumor of the gallbladder, 3 mm. in diameter, which was found in a chronically diseased gallbladder with stones removed at operation. This was the third case to be reported in which carcinoid involved this organ. Miller and Hermann (7) reported a case of carcinoid tumor of the jejunum and one of the upper ileum in 1942. Both of these cases had symptoms of partial obstruction. Five cases have been reported in which a carcinoid tumor had developed in the cecum without relation to the appendix or ileum (8). The lower ileum and appendix have been found to be the most frequent primary site of such tumors; 85 per cent of 283 recorded cases (8).

The clinical symptoms observed in patients suffering from carcinoid disease have as a rule been cramping abdominal pain, abdominal tenderness and irregularly recurring constipation and diarrhoea. Blood in the stools has been frequently noted and in different series symptoms of intestinal obstruction have been present in from 17 to 24 per cent (9). When the primary lesion has been localized in the appendix, symptoms of acute or recurring attacks of appendicitis have led to early operation (1). Later in the course of the disease added symptoms due to metastases have occurred in from 24 to 52 per cent of the cases in different series (9). The symptoms present in our patient were essentially those of chronic pellagra. There were present the fiery red glossitis and pharyngitis, pigmentation of the hands, forearms and face, bilateral patches of dermatitis about the knees, and frequent watery stools were passed from 6 to 8 to 20 times a day; always foul and watery in character, and containing no

¹ The terms carcinoid and argentaffinoma have been used interchangeably. Ritchie and Stafford (4) have suggested the names benign argentaffin tumor and argentaffin carcinoma. Hopping, Dockerty and Masson (11) consider them adenocarcinoma grade I (Broders). The tumor was first described by Langhans (12), (1867); again by Lubarsch (13), (1888). Bunting (14) described the tumor first in this country (1904) and Obendorfer (15), (1907) first used the term carcinoid.

abnormal fat. Blood was not found in them until shortly before death. A severe proctitis added to the patient's suffering although marked depression was present at all times. With the absence of distinctive gastrointestinal roentgenological findings, the clinical diagnosis was pellagra of undetermined cause.

CASE HISTORY

C. E. R., white, male, aged 65, watchman by occupation, entered the Royal Jubilee Hospital on the service of Dr. T. Miller, February 20, 1945, and died in hospital July 29, 1945. He had suffered with persistent diarrhoea, bloating, cramping abdominal pain and increasing weakness and lethargy for eight or nine months before entrance. This condition continued progressively to the end. Prior to 1919 the patient had been a stoker in the Royal Navy, and as such he had visited all parts of the world, including Africa and the Orient. He contracted malaria in Africa but had no other tropical diseases to his knowledge. He had had some of the childhood fevers, repeated attacks of tonsillitis until his tonsils were removed in 1931. He was operated upon for a ruptured appendix in 1921, and eighteen months later an abscess was drained from the lower end of the abdominal incision. In hospital detailed examination failed to reveal the cause of his illness. He presented the picture of pellagra; namely, mental torpor, fiery red glossitis and pharyngitis, pigmentation of the hands, forearms, neck and face and patchy dermatitis about both knees. The abdomen was tympanitic, doughy to the feel, without tumor masses and very tender. There was moderate edema of the rectal and sigmoid walls and local proctitis, but no ulceration and no bleeding points. As many as 20 stools, watery, foul, and light greenish in color, were passed per day. They contained no fat, no amoebae or other parasites, and were negative to all members of the dysentery group of organisms. Blood was absent until the final days when 1+ and 2+ reactions with benzidine were obtained. An Ewald meal showed no free acid. The blood showed a hypochromic anemia which varied by reason of repeated blood transfusions. In the latter days, there was a hemoconcentration up to 17.8 grams hemoglobin per hundred cubic centimeters of blood. The sedimentation rate of the red blood cells varied from 0 to 20 millimeters in one hour. The white blood count varied from 5,400 to 20,600 cells per cubic millimeter, of which 52 to 83 per cent were polymorphonuclear neutrophiles. The eosinophiles were not increased. A moderate degree of soft pitting edema was noted universally over the legs and dependent parts of the trunk. Roentgen ray examination of the gastrointestinal tract and gallbladder were negative except for a general hypermotility of the former. There was no evidence of obstruction. There was no evidence of metastatic malignancy noted in the vertebrae. Intensive anti-pellagra treatment, including anterior pituitary hormone, did not influence the progressive course. He had lost from 189 pounds to approximately 100 pounds at death.

GROSS PATHOLOGICAL FINDINGS

The body was that of an emaciated, rather poorly developed white male, 65 years of age, 110 pounds in weight and 5'5" (165 cm.) in height. The teeth were missing,

the gums were swollen and purple red, the throat was injected, there were no masses palpable in the cervical, axillary or inguinal regions. The skin over the forearms showed considerable brownish pigmentation. The lower extremities distal to the knee joints were edematous. Bed sores were present over the sacrum and the left buttock. The pericardial sac contained approximately 25 cc. of clear straw colored fluid. The surfaces were normal.

The heart weighed 290 grams. The right ventricle measured 0.3 cm. in thickness and was slightly dilated, the left ventricle measured 1.3 cm. in thickness. The muscle was softer than normal in consistency. No lesions were noted on section. The cardiovascular system was otherwise normal. Each pleural cavity contained 1500 cc. of clear straw colored fluid. The pleural surfaces revealed no lesion. The right lung weighed 500 grams and the left 240 grams. Congestion and atelectasis were present in each lung. The bronchi contained watery mucus material.

The peritoneal cavity contained 2000 cc. of slightly turbid yellowish fluid. Tumor nodules were present beneath the capsule of the enlarged liver.

The esophagus and stomach were free from lesion. The mucosal surface of the small intestine revealed numerous tumor growths which were situated both in the ileum and jejunum, the greater number being present in the former. There were approximately 50 tumors noted. They appeared to be situated beneath the mucosa and measured from 0.4 cm. to 2 cm. in diameter. The smaller growths were split-pea shaped and bulged inwardly beneath the mucosa. The larger were flattened. Many had the appearance of a lily pad, the edges being somewhat slightly raised. On section, the growths were yellowish white in color and sharply demarcated from the surrounding submucosa in which they lay. They were fairly firm in consistency. The largest growth was situated 20 cm. from the ileocecal junction. This was the only growth in which the mucosa on the surface was ulcerated. Throughout the mesentery the lymph nodes were enlarged to as much as 2 cm. in diameter. All these on cut section were firm in consistency, yellowish white in color and homogeneous.

The appendix had previously been removed. The cecum and the remainder of the large intestine contained no tumor growths. The mucosa appeared to be slightly edematous.

The liver weighed 1800 grams and measured 21 x 20 x 11 cm. Beneath the capsule were numerous white yellow areas of tumor growth, and on section 50 per cent of the liver substance was occupied by round discrete masses made up of yellow white tissue which was firm in consistency and homogeneous in appearance. These masses varied in size from 0.3 cm. to 5 cm. in diameter. Certain of them were degenerated, soft and slightly hemorrhagic, others showed beginning degeneration but this was not the usual finding.

The gallbladder and associated bile ducts were patent throughout.

The pancreas and adrenals were entirely normal grossly.

The spleen weighed 150 grams and measured 10.5 x 7 x 4 cm. Its capsular surface was normal but its cut surface was firm with increased trabeculation.

Each kidney weighed 150 grams and appeared normal except for congestion.

The bladder and genitalia were normal.

The abdominal lymph nodes apart from the mesenteric nodes mentioned above were free from lesion.

MICROSCOPIC OBSERVATION

Lying in the submucosa of the small intestine were growths made up of masses of spheroidal and polyhedral cells with small amounts of granular cytoplasm and nuclei, which were regularly staining and somewhat irregular in size. These masses were fairly discrete, were well separated by strands of fibrous tissue and were typical of a carcinoid tumor. The growth in instances extended into the mucosa and in one area ulceration had occurred on the surface exposing the growth to the lumen. The muscular coat was invaded. Here the tumor cells were lying in cords and this invasion appeared to have reached the serosa. Further sections of the small and large bowel showed only edema of the mucosa.

The liver contained many secondary carcinoid tumor growths. The tumor cells similar to the growth described above lay in irregularly shaped masses which were separated by fine strands of connective tissue. There was a suggestion of "pressure capsule" formation in the liver substance in approximation to the secondary malignant masses, but here and there infiltrations extended out into the liver. These were less clumped and the cells often were more scattered. The uninvolved liver substance showed central congestion with dilatation of the sinusoids and cloudy swelling and fatty degeneration of the peripheral liver cells. There was no suggestion of cirrhotic or of any inflammatory process, it being a picture of chronic passive congestion.

The spleen was markedly congested, the sinusoids being stuffed with red cells and the pulp suffering correspondingly. Blood pigment was present in the reticulo-endothelial cells.

Chronic passive congestion and terminal bronchopneumonia were present in the lungs.

Outside of postmortem change and slight atheroma of the vasculature, the other organs and tissues did not reveal any significant changes.

CONCLUSION

Multiple growths of the small intestine presenting a typical histological picture of a malignant carcinoid tumor with secondary involvement of regional lymph nodes and liver were found at postmortem. Pellagra was evidenced by the pigmentation of the skin, the mouth and tongue lesions, and by edema of the intestinal mucosa. Fatty change was not marked in the liver except as accompaniment of chronic passive congestion.

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AN ULCER WHICH APPEARED IN THE STOMACH OF A MAN RECEIVING HISTAMINE INTRAVENOUSLY

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Many reports of the production of peptic ulcers in experimental animals have appeared in the literature in the past twenty-five years. The most instructive study, relative to our report, has been that of Hay, Varco, Code and Wangenstein (1) in 1942. They reported the production of peptic ulcers in experimental animals by using a mixture of histamine and beeswax. By daily intramuscular injections of this mixture, they were able to produce peptic ulcers in thirty-five of fifty-two experimental animals of various types. From their observations of the experimental animals these authors felt that the acid is the important factor in the production of peptic ulcer in man.

As far as we know, there is no report in the literature of the experimental production of gastric ulcer in man. While it is true that McHardy and Browne (2) report the occurrence of duodenal ulcers in two persons who previously had been desensitized to histamine, there is no definite relation between the discovery of the duodenal ulcers and the previous desensitization to histamine. We felt, therefore, that the report of a case in which an ulcer appeared in the stomach of a man receiving treatment with intravenous doses of histamine might be of interest. One of us (B. T. H.) has been making wide use of histamine intravenously as a therapeutic agent since November, 1939. It has always been our custom to instruct patients to eat immediately before reporting to the laboratory for the injection. During the years we have had no case in which we suspected that an ulcer formed during treatment. In this particular case it may be significant that the patient was under the impression that he had to report each morning with an empty stomach (3). It may be that this was the reason why in this patient an ulcer formed in the stomach.

REPORT OF CASE

A white man, twenty years of age, registered at the Mayo Clinic on July 14, 1943. For two years he had been suffering with symptoms typical of multiple sclerosis.

Intravenous administration of histamine was started on July 22, 1943. The solution used consisted of 2.75 mg. of histamine diphosphate (1 mg. histamine base) in 250 c.c. of physiologic salt solution. It was injected at the rate of 2 c.c. per minute (0.009272 mg. of histamine base per minute). The injection which lasted approximately an hour and a half was repeated each morning at a progressively faster rate,

until 3.5 c.c. per minute (0.016226 mg. of histamine base per minute) was being administered.

Subjectively, he stated that his neurologic symptoms were improving rapidly. However, on the evening of August 11, after the eighteenth intravenous injection of histamine had been administered, he suddenly became nauseated and vomited blood-streaked material. On the next day (August 12), he vomited twice, before and after breakfast, and appeared later at the laboratory complaining of nausea, weakness and general malaise. Because of the suspicious symptoms, histamine therapy was discontinued and the patient was instructed to eat five small meals per day. On August

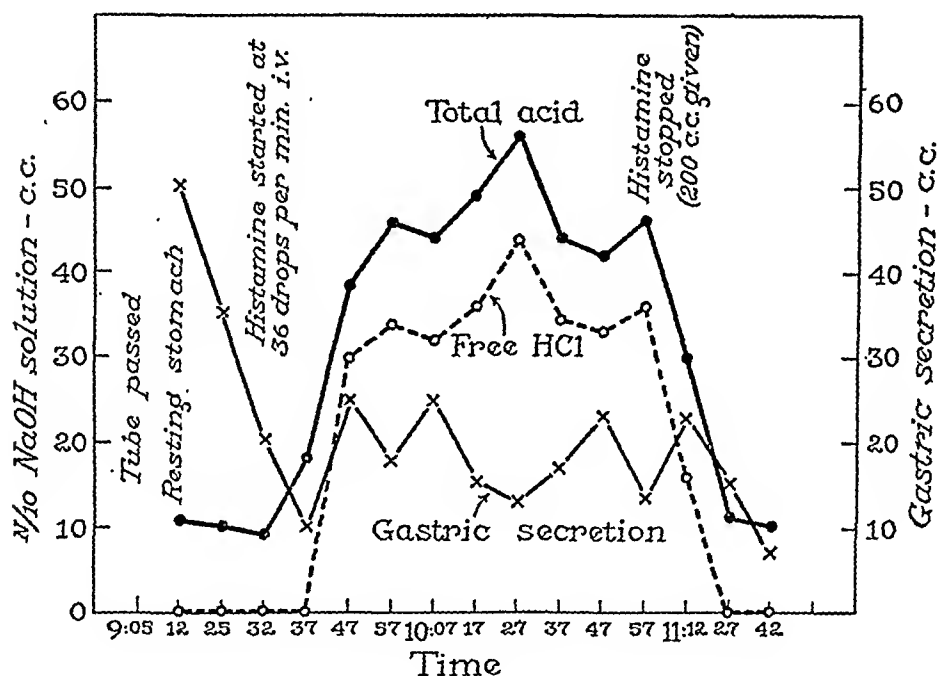


FIG. 1. GRAPH ILLUSTRATING THE RESPONSE OF THE ACIDITY AND VOLUME OF GASTRIC JUICE AFTER THE CONTINUOUS INTRAVENOUS ADMINISTRATION OF HISTAMINE

13, a fluoroscopic study of the stomach and duodenum revealed a small gastric ulcer in the lesser curvature below the angle. Nausea and malaise continued until August 16, when the symptoms disappeared. No other therapeutic measures were considered necessary at this time. On August 24, a roentgenologic study of the stomach and duodenum showed no sign of the ulcer.

On August 27, the response of the acidity of the gastric contents to the intravenous administration of histamine was determined. The results are shown in figure 1. The curves are normal and are similar to those one of us (B. T. H.) has observed in twenty-seven cases of multiple sclerosis in which a similar study was made. The neurologic examination revealed a complete disappearance of all subjective and objective symptoms except an occasional tremor of the right hand.

COMMENT

As already noted, this is the first time we have encountered peptic ulcer after the intravenous administration of histamine although one of us (B. T. H.) has supervised the giving of more than thirty-eight thousand such injections during the past six years. Furthermore, some patients have received as many as 300 injections without any noticeable ill effects. We have been aware of the fact that a minimal amount of histamine given intravenously produces for the most part a maximal rise in the gastric acidity. Hence we have always insisted that patients eat immediately before treatment is started. It is interesting that in this case the stomach was empty when the histamine was injected and that an ulcer developed after the eighteenth injection. This was in spite of the fact that the drug was administered for only one and a half hours each day; in the case of the animals used by Hay, Varco, Code and Wangensteen, histamine was given steadily for a period of several days.

SUMMARY

This report concerns the appearance of a gastric ulcer in a man, aged twenty years, who had multiple sclerosis and who was being treated by the daily intravenous administration of histamine. Perhaps because this patient had neglected to eat immediately before each injection, a gastric ulcer formed. The injection of histamine was promptly discontinued and the ulcer healed in twelve days.

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EDITORIALS

UPON THE OCCASION OF THE 10TH ANNIVERSARY OF THE DEATH OF I. P. PAVLOV

Pavlov was outstanding among present day physiologists. This was officially recognized at the 15th International Physiological Congress at Moscow in 1935, where he was pronounced the "first of the world's physiologists" ("princeps physiologorum mundi"). From the beginning to the end, his life was filled with untiring and very fruitful work. He died February 27, 1936, from "flu," at the age of 86 years and 5 months. Only four days before his death he gave a report of his latest data on the treatment of some psychiatric disturbances to the Russian Psychiatric Society. Up to his death he was the head of four Russian physiological laboratories and had over fifty assistants working under his direction.

Ivan Petrovich Pavlov was born September 27, 1849, at Riazan, about 150 kilometers south of Moscow. His father was a priest and his grandfather a sexton; his mother's family were also of the clergy. Pavlov received a religious education at a seminary and then graduated from the University at St. Petersburg, majoring in chemistry and physiology. Finally he took a medical course at the Military Medical Academy. For ten years he was assistant and had charge of the research laboratory of the famous St. Petersburg clinician, Dr. S. P. Botkin. He completed his education in Germany working two years in the laboratories of Heidenhain (at Breslau) and Ludwig (at Leipzig). In 1890 he was appointed Professor of Pharmacology at Tomsk in Siberia and also at the Military Medical Academy of St. Petersburg. He selected the latter. The same year, Prince Oldenburg organized in St. Petersburg the Institute of Experimental Medicine of which Pavlov's laboratory was a Department. In 1895, at the age of 46, Pavlov was appointed Professor of Physiology at the Military Medical Academy which chair he occupied during 28 years.

Pavlov's contributions to the physiology of digestion and his discovery of the conditioned reflex and its implications are known to every modern student of medicine and psychology.

Pavlov's works were widely recognized in his country and abroad. The first honor came from Mexico in 1898. In 1904 he received the Nobel prize for his studies on digestion. He was an honorary member of Academies of Sciences throughout the world.

Pavlov was very happy in his life and work. Throughout his long life he worked hard and successfully. He was a favorite of both the Czar and the Soviet government; both spent great amounts of money on his experiments.

Pavlov is a star which lights the science of physiology and shines down vistas still unexplored.

W. N. BOLDYREFF

BENADRYL: A NEW ANTIHISTAMINIC DRUG

In the November 14, 1945 number of the Proceedings of the Staff Meetings of the Mayo Clinic is the report of a symposium on the effects of a new and apparently valuable antihistaminic drug called "benadryl." It was synthesized by Parke, Davis and Company and chemically it is beta dimethylaminoethyl benzhydryl ether hydrochloride. Its pharmacologic action was reported on by Loew, Kaiser and Moore in February, 1945.

In the Mayo Clinic symposium C. F. Code described a number of efforts by chemists in recent years to find a drug that will combat or prevent the unpleasant actions of histamine in the body. A number of effective substances have been found but most of them have proved a bit too toxic for general use. Some are promising but haven't yet been sufficiently tested.

Benadryl shows only slight toxicity in animals, but in man it has a few disturbing actions such as the production of drowsiness, dizziness, dry mouth, nervousness and urinary frequency.

In the symposium McElin and Horton reported definite signs that the drug has antihistaminic effects. In their hands it helped twenty-one of twenty-two patients with hay fever and seven of eight patients with vasomotor rhinitis. It did not help three patients with migraine and seven with atypical pains in the face and head. The drug did help four of eight persons with a histaminic headache and four with a tension headache and vasodilation; it did not help two of three patients suffering from asthma.

The dose given by mouth ranged from 50 to 500 mg. per day; by intramuscular injection the dose was 20 mg., and by intravenous drip from 10 to 120 mg. was given during ten minute periods. The fluid used contained 60 mg. of the drug per 100 c.c. of physiologic saline solution.

Some of the case reports published by McElin and Horton are striking and very encouraging. Efforts to lower gastric acidity with the drug have not yet been promising because in a considerable number of cases the secretion of acid was increased by the drug. It did not consistently lower the acidity produced in man by injecting histamine.

O'Leary and Farber who used the drug in the department of dermatology were enthusiastic about the prompt relief seen in the cases of nine of fifteen patients with acute urticaria. Twenty-five of thirty-five patients with chronic urticaria and often angioneurotic edema were promptly relieved. Disturbing reactions were reported by some of the patients who took 100 mg. three or four

times a day; there was little trouble when the dose was half of this. The drug was more often palliative than curative.

Koelsche, Prickman and Carryer reported on the use of benadryl in the treatment of eighty-three patients suffering from hay fever and/or asthma. Sixty-nine per cent were helped. The greatest number helped were suffering from hay fever alone. Only one in three of the persons who had asthma alone was helped.

Williams, an otolaryngologist, found that about half of the patients suffering from sore head muscles were helped. Ten of twelve patients with vasomotor rhinitis were almost cured during the period of observation.

Logan, a pediatrician, found the drug helpful in a few cases of hay fever and one of asthma. He suggested a dose of 2 mg. per pound (0.5 kg.) of body weight.

Doubtless the drug will soon be widely used and there are reasons to hope that it will be of value in the treatment of a few diseases.

W. C. A.

COMMENT

THE INADVERTENT INTENSIFICATION OF NEUROSES BY PHYSICIANS

How often it happens that a physician comes to rue the unguarded moment in which he mentioned to some highly worrisome and perhaps psychopathic woman her harmless old heart murmur, her slight electrocardiographic change, her tiny colonic diverticulum, her chronic mastitis, her low blood pressure, or her small uterine myoma. As day after day he tries by the half-hour to undo the damage he did in a moment, as he explains and argues and tries to avoid the patient's efforts to trip him up and confound him with his own statments, he curses the moment when he put the trouble-making idea into her head.

If this can happen, as it commonly does, to the wisest and most tactful of physicians, to those who have learned the advantages of taciturnity, who are always guarding the tongue and who have learned to recognize quickly the type of patient who will instantly seize on the slightest word that can be used as a starting-point for insane worry, how often must it happen to the younger physician or the tactless one; the one who does not yet know when to watch his step, or the one who loves to tell his patients of all the awful diseases their symptoms are bringing to his mind.

Recently, in the "New England Journal of Medicine" there appeared a most thought-producing Harvard lecture by Ben Ames Williams, the writer, who pointed out the unwisdom of frightening patients and filling their minds with new fears.

Some years ago Sir Arthur Hurst wrote interestingly of what he called "iatrogenic diseases"—those common ailments that are implanted in the minds of patients by unwary physicians. Most of us doctors produce these diseases thoughtlessly and unconsciously: we just forget. A few of us produce them because we are pessimists, or because we really believe that the little bodily peculiarities which we call to the patient's attention do explain his symptoms and require treatment, or because we do not dare risk our reputation by failing to mention some harmless variant which may later be found and mentioned by some critical competitor, or because we feel we must in every case make a diagnosis of some organic disease, or because we think that when the patient recovers from the serious disease named, he or she will be impressed with the wonderful nature of the cure that was wrought. Whatever the reason, the result is often bad and sometimes it is tragic.

Today neuroses may be produced simply by following the modern custom of handing the patient copies of all the reports that came in during an elaborate

overhauling; often the practice is harmless and commendable; often it cannot be avoided, and then in an occasional case it may have tragic consequences. Some physicians alarm their patients needlessly because, in medical school, they were never trained to recognize the psychopathic type of worrier who, once scared half to death, can be reassured only by an expert using the greatest effort and skill. The few faddists who make the same diagnosis in most of their cases also cause much trouble by telling a harmlessly insane woman that all her symptoms are due to a low blood sugar or brucellosis or amebiasis. This sort of thing is bad if only because for a time it hurts the reputations of those able doctors in the community who made the correct diagnosis of a neurosis.

To get a glimpse of what is happening every day, now in every large city of this land one need only read the following letter just received from an intelligent professional man of scientific training who, for years, has known the misery of living always on the borderline of insanity, and who during all this time has earned his living each day only by gritting his teeth and fighting back his fears. In this struggle he has been greatly helped by a fine old family doctor who, knowing well the nature of the man's real disease and remembering his insane heredity, has kept him going on large doses of reassurance, and has frequently steered him away from specialists who, in any one short interview, might easily have failed to recognize the basic psychoneurosis and might thereby have done harm. Following is the letter:

"Dear Doctor:

After consulting you last October about my stomach I took your advice and put myself in the hands of a psychiatrist who has helped me a good deal. All went well until last month, when still feeling bad in my stomach and remembering that I had been taking a little wine to help my appetite, it occurred to me that I might have been producing an alcoholic gastritis, and so I went to one of the leading gastroscopists in this great city. He examined me and reported a mild superficial gastritis with a small mucosal hemorrhage.

"Since you know how exceedingly apprehensive a person I am, you can imagine how upset I was by the finding of a hemorrhage. That word terrified me and since hearing it I have had no peace or rest.

"On seeing my great alarm, the gastroscopist was sorry that he had frightened me and with great kindness he explained again and again that what he had seen did not have any serious significance; as he said, he finds such little changes in half of his routine examinations and even in those made in the case of apparently normal persons. He told me to forget it all and to go ahead and eat everything except duck and pork. However, I remained so anxious and upset that soon I was too ill to eat anything solid.

"I then went to the library to look up gastritis and finding there that the treatment for the disease resembles that for ulcer, for a while I took nothing but milk. But soon I got so weak that I had to eat more. About the only nourishing food that I am now

taking is a little meat extract with some puréed vegetables which the gastroscopist said I might have.

"As a result of all this I am now in a highly nervous state much worse than before and I am still losing weight. I have lost all the benefit I received from the treatment by the psychiatrist and I feel that something new will have to be done for me. I do hope now that you can assure me that I am in no danger from the mucosal hemorrhage and that you will tell me that I can begin to eat some regular food. I am so much worse off than when I started treatment for the gastritis that I am beginning to suspect that all my symptoms are due to a flare-up in my old psychoneurosis."

How beautifully this man has painted the picture of the psychopath who just has to keep getting himself examined although he knows that he will go to pieces nervously if the slightest thing wrong is ever found. In this case little blame can, of course, be attached to the gastroscopist; one can see how sorry he is for what he did. The suggestion that this experience has probably brought to his mind is that in future it would be wise, before examining anyone, to consult with the attending physician. If in this case the gastroscopist had only discovered that the man was under the care of a psychiatrist, and on getting in touch with that person had learned that there was no good reason for performing gastroscopy and many good ones for not making the examination, he could either have refused to make it or else he could have been forewarned to report a "normal stomach," granting, of course, that no serious lesion requiring treatment was found. Considerations like this apply of course, not only to gastroscopists but to all other special examiners whose training has not prepared them to be always on the alert to recognize the anxious insane.

This letter is published here not with any idea of blaming anyone—but only with the hope of starting specialists to thinking and to vowing that in the future they will do everything possible to avoid this type of tragedy, so annoying and time-consuming for themselves and so trying to the patient and his regular medical counsellors.

W. G. A.

BOOK REVIEWS

TRICHINOSIS. *By Sylvester D. Gould, M.D.* Charles C. Thomas, Springfield, Illinois, 322 pp. \$5.00.

This is an interesting and nicely illustrated monograph on an important subject. When human muscle obtained at routine necropsies is studied carefully it is found that about one in six Americans has at some time suffered from trichinosis. In many cases the infestation was probably too light to produce symptoms, and in other cases the illness was never properly diagnosed. It is astounding to read that in some cases pork has been so heavily infested with the little worms that a person who only tasted the material died. With a moderate human infestation one can find from fifty to 100 larvae in a gram of muscle. Over 1,000 larvae per gram will cause a serious situation.

The commoner symptoms in the order of frequency noted in an epidemic of 280 cases were soreness of muscles, hardness and stiffness of muscles, edema of the extremities, diarrhea, bronchitis, pain on swallowing, dyspnea, hoarseness, skin rash and vomiting.

A rapid pulse is a bad sign. When death occurs it comes usually in the fourth or fifth week of the disease.

As yet no drug has been found that will kill the larvae in the wall of the bowel or in the muscles.

Obviously, it is highly important that all pork be thoroughly cooked. The larger the mass of let us say a ham, the longer it must be cooked so that the heat can penetrate to the material in the center.

FOUNDATIONS OF NUTRITION. *By Mary S. Rose.* 4th Ed. Revised by Grace Macleod and Clara Mae Taylor, Macmillan Co., N. Y., 1944, 594 pp., \$3.75.

This is an attractive book which evidently has served its purpose well. It covers the subject and is full of up-to-date information.

THE EFFECT OF SMALLPOX ON THE DESTINY OF THE AMERINDIAN. *By E. Wagner Stearn and Allen E. Stearn.* Bruce Humphries, Boston, 153 pp., \$2.50.

Two lay persons concerned about the problem of vaccinating or not vaccinating their children very sensibly went to the library to get the facts. Soon they were fascinated to see what a terrible scourge smallpox can be when it attacks a community or a people who have not been immunized in some way against it. They became so particularly interested in the awful ravages that smallpox worked among the aborigines of America that they spent a year in big libraries gathering the facts. With these in hand they have written a book which will be of great interest to the anthropologist, the ethnologist and the epidemiologist.

In this book they show that again and again during the 450 years that have elapsed since the arrival of Columbus, millions of the aborigines have been swept away by smallpox. Often thousands would die within a few weeks after their contact with an infected white man, and commonly from 30 to 90 per cent of a tribe or "nation" would be wiped out. Often not enough were left to bury the dead.

In desperation the Indians and perhaps the missionaries with them would try out all sorts of remedies, but only when vaccination could be resorted to was an epidemic stopped.

In the face of such terrible evidence it is hard to understand how anyone today could advocate or fight for the neglect of universal vaccination. This can be done only by one who does not know what smallpox used to do and could still do. Especially convincing to persons who are in doubt as to the wisdom of vaccinating their children should be the fact that the writers of this book are not doctors of medicine, they are not even propagandists; they just published the facts that they dug out from old records and diaries of frontiersmen, and let these facts speak for themselves.

PATIENTS HAVE FAMILIES. By *Henry B. Richardson, M.D.* The Commonwealth Fund, New York, 1945, 408 pp., \$3.00.

As one would expect from the title, this is a book to call the attention of physicians to the fact that many of the troubles of patients are brought on by unhappiness and strain and poor adjustment at home. As Dr. Richardson says, this is "old stuff" to the general practitioner and family doctor who goes into the homes of his patients. If he is at all observant he knows what influences—good and bad—are to be found there. If a girl is brought in because of anorexia nervosa, he knows perhaps of the psychopathic heredity, and perhaps of the sex-hating and domineering mother who has just broken up the girl's first engagement. Unfortunately, the city internist knows nothing of this sort of thing unless he is interested enough to ask, and even then, the girl may be too secretive to tell him any part of the all-essential story.

As Dr. Richardson says, of late, medical leaders have been urging the medical practitioner to treat the patient and not the disease, but now the campaign must be extended and physicians must be reminded that often the family must be treated too. When a clinical history becomes too "fat" it is high time to send an investigator to the home to see what is wrong there.

Even when a disease is as definitely organic as scabies it is foolish to try to cure the patient alone—one must treat the family at the same time.

Dr. Richardson tells how, during his student days in clinic and hospital, "so far as I can recollect, [never] did anyone bring to my attention the influence of emotional stress in illness." Today, fortunately, psychiatrists are coming into clinics and wards, trained investigators are going out into the patients' homes, and a better era is dawning. Unfortunately, as yet, it hasn't had much influence on the practice and thinking of city internists and surgeons. As Richardson says, the city consultant usually sees the patient alone—and worse yet—the patient commonly fails to discuss or even conceals the most important facts about the origin of his illness. Time and again, when Richardson sent an investigator to a home to talk to the patient's family, it was found that the person who had been quiet and sensible and well-behaved in the office was violent and evidently not entirely sane at home.

The book could profit from a "boiling down" process, but it is full of meat, and it would be well if every internist and surgeon in the land would read it.

MAJOR PAUL MITCHELL GLENN, M.C., A.U.S.

Doctor Paul Mitchell Glenn, Major, A.U.S., died of disseminated lupus erythematosus at the Lawson General Hospital, Atlanta, Georgia, December 21, 1945, while on active duty in the service of his country.

Doctor Glenn was born in Cleveland, Ohio, July 9, 1906. He received his premedical education at Ohio State University, his medical degree from Western Reserve University in 1935 and served his internship in the University Hospitals, Cleveland, 1935 to 1937. After completing his internship, he obtained a fellowship in the Gastro-Intestinal Section of the Medical Clinic in the University Hospitals of Pennsylvania where under Doctor T. Grier Miller he became interested in the intubation studies of the small intestines, and in collaboration with the late Doctor Williams Osler Abbot and his associates, he published his first papers. In 1938 he returned to Cleveland to become a teaching fellow in medicine in the University Hospitals. He was appointed instructor in medicine in 1940 and senior instructor in 1941 at his Alma Mater. He was made physician-in-charge of the Gastro-Intestinal Clinic in Cleveland City Hospital, 1941.

Upon American entry into the war, he enlisted in the Army Medical Corps and was attached to the Fourth General Hospital in Melbourne, Australia until illness forced his return to the States in 1943. Since his return he has been at the Finney General Hospital, Thomasville, Georgia, where he was assistant chief of the Medical Service until the time of his death.

He was a member of Alpha Omega Alpha, certified by the American Board of Internal Medicine, Associate American College of Physicians, a member of the American Gastroenterological Association, the American Federation for Clinical Research, and fellow in the American Medical Association.

Although Doctor Glenn's medical career was cut short by his untimely death, he accomplished much. He was a well trained clinician, a good teacher, and took an active part in clinical investigative work, particularly problems relating to the gastro-intestinal tract. In the death of Doctor Glenn the American Gastroenterological Society has lost one of its most promising young members.

A. J. BEAMS



MAJOR PAUL MITCHELL GLENN, M.C., A.U.S

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STOMACH

BENEDICT, E. B. AND SCHWAB, R. S. Gastroscopic studies in naval personnel with chronic seasickness. *New Eng. J. Med.*, 233: 237 (Aug.) 1945.

In a group of 150 cases of chronic seasickness studied clinically at the United States Naval Hospital in Chelsea, Massachusetts, routine gastrointestinal X-ray studies showed that 50% had a characteristic roentgenologic appearance. These cases showed a constant triad of findings, namely, hypersecretion, loss of gastric motility, and spasm of the pylorus. When a thickened barium solution was used to bring out the gastric rugae, there was evidence in a few cases of a moderate degree of hypertrophic gastritis. In order to confirm these findings, direct gastroscopic examination was made. The result of the gastroscopic examination in 22 men showed moderate hypertrophic gastritis (1 case), moderate superficial gastritis (2 cases), slight superficial gastritis

(3 cases), gastric spasm without gastritis (2 cases), and a normal stomach (14 cases). In discussing their findings, the authors state "the thickened rugae observed by X-ray examination in many of these cases were not confirmed by gastroscopy and cannot be considered as positive evidence of gastritis."

IRVING GRAY.

ARENDT, J. Chronic hypertrophic antrum gastritis. *Ann. Surg.*, 122: 235 (Aug.) 1945.

Roentgenologic differentiation between hypertrophic gastritis, peptic ulcer, and malignancy of the antrum is difficult because of certain features held in common. The author estimates that the errors may be as high as 20%. Seven cases are presented briefly. Antrum hypertrophy and spasm, invagination of the bulbar base, and delayed opening of the pylorus are common findings in antrum gastritis. It is recom-

mended that surgical intervention be not delayed in doubtful cases.

LEMUEL C. MC GEE.

WAY, S. Relation between gastric acidity and the anterior-pituitary-like hormone content of urine in pregnant women. *Brit. Med. J.*, 4414: 182 (Aug.) 1945.

The gastric juice is reported as low in pregnancy, rising somewhat in the last weeks and rising sharply after childbirth. Way had noted hyperemesis gravidum in association with hydatiform mole. Recognizing an association of mole with the anterior pituitary-like hormone in the urine, he studied the correlation of the acidity of the gastric juice with the presence of hormone in the urine.

Histamine was not used and the figures of the analyses are not given. In early pregnancy, 8 to 16 weeks, the maximum HCl titration was 0.023%. In the 20 to 29 week period the maximum HCl was 0.045%. A 35 to 40 week group showed a maximum HCl of 0.079%. A group of patients with positive Aschheim-Zondek test in 1:10 dilution showed a maximum HCl of 0.029%; a second group, positive 1:5 dilution but negative 1:10, showed a maximum of 0.044%. A third group with positive Aschheim-Zondek, but negative at any dilution, showed a maximum HCl of 0.079%. Way thinks there appears to be some relation between acid values of the gastric juice and the amount of anterior pituitary-like hormone in the urine, and that the relation is inversely proportional.

MILLS STURTEVANT.

THOMAS, S. F. The value of gastric pneumography in roentgen diagnosis. *Radiol.*, 45: 128 (Aug.) 1945.

Pneumography of the stomach was first introduced by Engel and Lysholm in 1933. The present author changed the method by the use of a small caliber stomach tube, which served first for aspiration of gastric contents and then inflation of the stomach. The patient is laid prone, with high supports under the chest and pelvis. This is done to insure a normal contour of the posterior wall of the stomach, which silhouettes the retrogastric space. The beam

of the X-rays is horizontal, and a vertical Bucky diaphragm is used. The amount of air is not predetermined but is governed by the ability of the patient to restrain regurgitation. The quantity is between 300 and 800 cc. The purpose of the immediate exposure of the films is to avoid filling the upper small bowel with air. The author believes that this method is of supplementary diagnostic value in the location and diagnosis of enlargement of the body or tail of the pancreas, and of aid in the localization of certain epigastric masses.

FRANZ J. LUST.

MILLER, R. F. AND OSTRUM, H. W. Hypertrophic pyloric stenosis in infants. Roentgenologic differential diagnosis. *Am. J. Roent. Rad. Therapy*, 54: 17 (July) 1945.

The authors give the following reasons why a roentgen examination is not often made in hypertrophic pyloric stenosis: (1) history of bile-free vomiting with a palpable mass in the epigastrium and visible gastric peristalsis, (2) symptoms persisting after change of formula and administration of antispasmodics, (3) the objection of the use of barium for fear of aspiration, (4) a residue of barium interfering with nutritional requirements. Numerous factors influencing the emptying time of the normal infant's stomach are discussed. Emphasis is placed on the tendency toward delayed emptying if the patient is kept in the supine position, which interferes with the escape of gas from the stomach. It is noteworthy that gaseous distention of the stomach reflexly inhibits gastric peristalsis and delays motility. To eliminate the excessive gas, the patient is placed in the prone position. In pyloric muscle hypertrophy there is no variability in the length of the prepyloric segment and no cycles of gastric motility. The pyloric segment is longer and the lumen narrower than normal. The projection of barium from the pyloric canal depends upon the degree of narrowing. Vomiting usually occurs from the third to the fifth week of life, and as a rule obstruction is incomplete. When the barium enters the small intestine, the intestinal loops are not continuous, presenting a segmented pattern.

The authors have studied the gastrointestinal tract in 50 infants. The amount of gastric retention depends upon the degree of pyloric narrowing. In marked cases there was as much as 80 or 90% retention. The duodenal cap never completely filled in a single instance, and was visualized only by a few specks of barium. The pyloric canal presents a beak-like projection pointing toward the cap. They demonstrated shoulders convexly directed toward the pars media. Emphasis is placed on those cases requiring surgery, which usually have an enlarged slightly atonic stomach. A narrowed pyloric canal, elongated beyond 0.5 cm., with a gastric retention of over 50% (usually 70-80%) at the end of 4 hours is strongly suggestive of this condition.

MAURICE FELDMAN.

HAMILTON, J. B. Gastric volvulus and other abnormal rotations of the stomach. *Am J. Roent. Rad. Therapy*, 54: 30 (July) 1945.

Any rotation of the stomach approaching 180 degrees, which spontaneously reduces itself, is reducible by manipulation, or the result of trauma, is considered a true gastric volvulus. The author reports 11 cases of gastric volvulus. All of these presented relaxed intra-abdominal attachments with various etiologic factors. Elevation of the left diaphragm was present in three. In two cases there was a herniation of the diaphragm. In one, a right sided thoracic stomach herniated through the foramen of Morgagni. A large redundant or abnormally situated colon was a feature in several cases.

While the symptoms were not characteristic, all of the patients presented signs of gastric disturbance. In 6 there was nausea and vomiting. In several of them there was a history of previous attacks with complete remission of symptoms between the attacks. Gastric volvulus is best seen under the fluoroscope in the upright postero-anterior position. Illustrations are presented of each case.

MAURICE FELDMAN.

BOWEL

DRUCKMANN, A., AND SCHIÖRR, S. The roentgenological manifestations of amebiasis of the large intestine. *Am. J. Roent. Rad. Therapy*, 54: 145 (Aug.) 1945.

Amebiasis of the colon occurs as a diffuse or localized condition. The diffuse type produces scattered lesions with a Roentgen picture simulating ulcerative colitis. The localized type give a more characteristic Roentgen picture. The two varieties may co-exist. Clark is quoted as having found an incidence of 60% diffuse and 40% localized. The following sites are noted, in order of frequency; cecum, ascending colon, sigmoid, and rectum. The amebic granuloma producing stenosis may simulate the picture of carcinoma. In amebiasis, the lesion is usually extensive and frequently multiple. The stenosis is usually incomplete. There is usually no pain elicited during the enema examination. The transition of the involved and normal segment is gradual and smooth. The stenosed lumen does not present a fixed rigidity of the wall. The mucosal relief of the involved segment is more or less regular. After anti-amebic treatment, the follow-up examination will show a restoration of the bowel to normal.

MAURICE FELDMAN.

BARBOSA, J., BARGEN, J. A., AND DIXON, C. F. Regional segmental colitis. *Surg. Clinics N. Am.*, 939 (Aug.) 1945.

Regional colitis refers to a non-specific ulcerative colitis, involving one or several segments of the colon as one continuous lesion or as a multiple involvement of the colon sparing the terminal portion (rectum). This type of colitis was found in 4% (140 cases) of 4,000 different cases of ulcerative colitis seen at the Mayo Clinic from 1923 to 1943.

The symptomatology of the regional type is frequently bizarre and varied. The diarrhea is rarely severe, but loss of weight is a common feature. Fever and cramps depend on severity. Blood and pus are much less frequent than in generalized ulcerative colitis. Ninety of the 140 cases were treated medically, 43 surgically, and 7

received no form of treatment. The surgical treatment of choice is radical surgical excision rather than short-circuiting or side-tracking procedures. In some cases medical regimen resulted in the complete relief of symptoms and objective signs of disease. Sulfaguanidine and succinylsulfathiazole were used with material benefit in the control of the active infectious phase of the disease.

FRANK G. VAL DEZ.

MOREHEAD, R. P. AND WOODRUFF, W. E.
Solitary giant follicular lymphoma of the vermiform appendix. *Arch. Path.*, 40: 51 (July) 1945.

Tumors of the vermiform appendix are not common. They are usually carcinoids. In 1926, Friend found but 19 cases of sarcoma of the appendix in the literature. The majority of these were lymphosarcomas and resembled histologically tumors of this type arising elsewhere in the body.

The author reports three cases with symptoms of acute appendicitis. One patient, a 33 year old negress, had had recurrent attacks; a white boy of 12 years and a white man aged 26 years were operated upon during the first attacks. In each instance the appendix showed a localized firm grayish-white tumor which was composed of lymphoid tissue. The latter was characterized by hyperplasia of the lymph nodes, disruption of follicular outlines, and invasion of all coats by large hypochromatic cells, smaller more chromatic cells, and medium sized lymphocytes. They were considered to be examples of giant follicular lymphoma with direct transformation into "polymorphous cell sarcoma". None of the patients had come to autopsy.

N. W. JONES.

LIVER AND GALL-BLADDER

CLAGETT, O. T. Diseases of the gallbladder: Diagnosis and management. *Surg. Clinics N. Am.*, 929 (Aug.) 1945.

Pregnancy is not thought to have any effect on the incidence of cholecystic disease. Women are, however, afflicted twice as frequently as men and at an earlier age. Cholecystography is an invaluable aid in

the diagnosis of cholecystic disease. In more than 90% of the cases of acute cholecystitis there is a past history of cholecystic disease, often with minor attacks of biliary colic.

As regards management, chronic non-calculous cholecystitis is best treated by conservative medical management. Chronic cholecystitis with stones invariably requires surgical treatment, regardless of the symptoms and age of the patient, provided, of course, the patients' general condition will permit surgical intervention. Acute cholecystitis in the first 48 hours is primarily obstructive rather than inflammatory, and therefore operation is the treatment of choice at this time. The operative procedure—that is, whether cholecystostomy or cholecystectomy is to be done—depends upon the ability and limitations of the surgeon and patient.

FRANK G. VAL DEZ.

NARAT, J. K. AND CIPOLLA, A. F. Fragmentation and dissolution of gall stones by chloroform. *Arch. Surg.*, 51: 51 (July-Aug.) 1945.

As a rule, mechanical means are sufficient for the removal of stones from the biliary tract. The field of usefulness of a chemical solvent is limited to two indications:

(1) "When a stone is firmly lodged in the common duct and cannot be removed manually, or when the surgeon is not certain that all broken particles of the stone have been removed. If the stone is firmly lodged close to the ampulla of Vater, use of a solvent may obviate the necessity of opening the duodenum."

(2) "When a stone in the hepatic duct slips away into the liver in the course of attempts to remove it mechanically."

If these conditions are present, injections of heated chloroform may be given a trial; apparently this method does not represent a therapeutic hazard. It is advisable to use only 5 to 6 cc. of the solvent and to pinch the hepatic duct during the procedure. In experiments in vitro as well as on animals, heated chloroform proved superior to ether as an efficient solvent for gall stones. Re-

peated injections of chloroform during the postoperative period are discouraged; they are not efficient and represent a potential hazard. Further observations are necessary before a final evaluation of this method can be made.

FRANCIS D. MURPHY.

STREICHER, M. H. Sulfanilamide-experimental production of liver damage: Its effect on gastric acidity. *Am. J. Dig. Dis.*, 12: 267 (Aug.) 1945.

Prolonged intragastric administration of sulfanilamide to dogs resulted in definite liver changes. Grossly, the liver remained unchanged, but the cellular elements of the liver were atrophic in nature. The amount of fat in the liver was not altered but there was a definite decrease of glycogen. A depression of gastric acidity was noted. Progressive damage to the liver inhibits the gastric secretory mechanism. Evidence from the author's experimental work supports the theory of idiosyncrasy.

H. J. SIMS.

WEIR, J. F. Tests of liver function. *Med. Clinics N. Am.*, 973 (July) 1945.

Weir lists and explains the tests of liver function used in the Mayo Clinic. These include the van den Bergh, bromsulfalein test, hippuric acid test, galactose tolerance test, urobilinogen in the feces and urine, blood serum protein, blood cholesterol and cholesterol ester concentration, blood urea, serum calcium, plasma chlorides and Hanger's cephalin-cholesterol test. He points out that, with 33 different known functions of the liver cells and at least 100 chemical activities, testing a single activity may not be clinically informative. His criteria for a practical liver test are that it can be readily performed, easily interpreted, reliable, and give worth while information from a diagnostic, therapeutic, or prognostic standpoint.

MILLS STURTEVANT.

COMFORT, M. W. Constitutional hepatic dysfunction. *Med. Clinics N. Am.*, 982 (July) 1945.

In 1902, Gilbert and Lereboullet described a clinical entity in which the bile pigment

in the blood was increased, without bile in the urine, with or without jaundice, and without enlargement of the liver and spleen. The condition was given the name of simple family cholemia. Comfort discusses the condition from his experience of 2 series of cases, previously reported.

The condition is characterized by increases in serum bilirubin—as high as 10 or 12 mg. percent. Red cell fragility is not increased. The indirect van den Bergh is positive. The diagnosis is made only after the exclusion of hepatic and hemolytic disease. Comfort thinks the disease mechanism involves an abnormally high excretion point for bilirubin in the hepatic cells. In one case, followed four years, the spleen became palpable and the erythrocytes became microcytic with increased fragility, suggesting some relation to chronic hemolytic icterus. In 30% of Comfort's cases cholecystic disease, with or without gall stones, was present. There is no treatment, but the prognosis is excellent. The diagnosis is important to prevent unnecessary treatment. The author prefers the name "constitutional hepatic dysfunction." There are fifteen references.

MILLS STURTEVANT.

BRANCH, A., TONNING, D. J. AND SKINNER. G. F. Adenoma of the liver. *Can. Med. Assoc. J.*, 53: 53 (July) 1945.

Benign liver cell adenomas may be subdivided into (1) the cholangiomatous type, resembling ducts; (2) the parenchymatous type, resembling liver columns; and (3) the mixed type, in which both kinds of formation occur.

A case is described in a 32 year old woman who had a mobile upper abdominal tumor, diagnosed before operation as a mesenteric cyst. An encapsulated adenoma was found within an enlarged right lobe of the liver. The right lobe of the liver with the tumor was removed at the level of the gall bladder, with uneventful recovery. Microscopic examination showed the tumor to be composed chiefly of unorganized masses of liver cells, with proliferation of bile ducts in some fields to give an appearance of lobulation suggestive of cirrhosis.

IRVING WOLMAN.

QUASTLER, H. Note on cholecystography with Priodax: Dosage and gastro-intestinal effects. *Radiol.*, 45: 190 (Aug.) 1945.

The gastro-intestinal side effects of Priodax used for cholecystography were studied in 100 cases. The author found that in high doses of Priodax such effects were produced. If 0.03-0.06 per pound body weight of the patient was given, it produced an average of 1.9 bowel movements per patient, and nausea in 11% of them. If the dosage was increased to 0.06-0.10 per pound, they averaged four bowel movements and 25% with nausea. By keeping the dosage below one tablet per 17 lbs., the gastro-intestinal effects can be held to a low level.

FRANZ J. LUST.

RICHARDSON, J. S., AND SUFFERN, W. S. A therapeutic trial of choline chloride in infective hepatitis. *Brit. Med. J.*, 4413: 156 (Aug.) 1945

Choline chloride (1.5 g. a day) was given to 16 cases of infective hepatitis, 16 other cases being used as controls. The diet was low in fat, high in carbohydrate. The criteria of therapeutic efficacy were: a drop in serum bilirubin to 0.6 mg. percent, bile-free urine, a return of appetite, and the patient could be allowed out of bed—all on the first day. In addition, the duration of stay in the hospital and the number of relapses were taken into account. No significant benefit as a result of treatment was noted.

MILLS STURTEVANT.

ANEMIAS

CLARK, R. L., JR., POWER, M., HECK, F. J., AND DIXON, C. F. Iron deficiency and anemia associated with carcinoma of the proximal portion of the colon. *Med. Clinics N. Am.*, 958 (July) 1945.

A study of anemia in 21 patients afflicted with carcinoma of the cecum and ascending colon is presented. Thirteen patients had carcinoma of the cecum: 5 in the ascending colon and 3 in the hepatic flexure. The ages were from 38 to 72 years. Fifteen of the patients had symptoms from 1 to 2 years or more.

The red cell counts were below four million in only 3 of the 21 cases. There was greater reduction of the hemoglobin proportionately. In 13 cases it was under 10 gm. per 100 cc. of blood. Microcytosis was found to some degree in 9 cases. Two of the patients had approximately normal blood values. In 19 cases there existed varying degrees of hypochromic anemia. The authors present evidence that the anemia is not of cancer toxin or bacterial toxin origin, but is due to blood loss with deficient intake or absorption of iron. Serum iron determinations seemed to confirm this. Two cases of cancer of the left colon also showed a similar anemia.

MILLS STURTEVANT.

GOTTLIEB, B. High-color-index anemia due to vitamin C deficiency. *Brit. Med. J.*, 4412: 119 (July) 1945.

Four severe cases of scurvy with macrocytic anemia, all male pensioners living alone, and all on diets moderately deficient in vitamin C, are reported. One died soon after admission but the remaining three responded satisfactorily to ascorbic acid on mixed hospital diet without liver, iron, or vitamin B complex. The red cell count on admission was 2,400,000, 2,080,000 and 1,700,000 in the three cases respectively; the hemoglobin was 60, 54 and 38; and the color index 1.25, 1.2 and 1.11. Capillary fragility was raised in each case but became normal in 3 to 6 weeks.

About 70% of all scurvy cases are anemic, the majority being normocytic although macrocytic anemia has been described in this association. The author suggests that this is a matter of severity. It is suggested that ascorbic acid therapy be tried in macrocytic anemia with diets deficient in vitamin C, particularly if there is hydrochloric acid in the gastric juice.

MILLS STURTEVANT.

RICHARDSON, J. E. Addisonian anaemia following entero-anastomosis. *Brit. J. Surg.*, 33: 71 (July) 1945

The report deals with a patient who had undergone a jejuno-colostomy. Five years later a pernicious type anemia developed with a high colour index, reticulocyte re-

sponse, and a typical blood picture. In this case the gastric fractional test-meal showed free and total acid to be present, with increased acidity after the first hour. The patient was suffering from a peptic ulcer of the duodenum, which bled during the stay at the hospital. The relief of the Addisonian anemia and of the fatty diarrhea, which followed the closure of the intestinal fistula, establishes the very interesting relationship between the fistula and the anemia.

FRANZ J. LUST.

ULCER

BLACK, B. M. AND BLACKFORD, R. E. Perforated peptic ulcer: Review of ninety-six cases. *Surg. Clinics N. Am.*, 918 (Aug.) 1945

A review of 96 patients with perforated peptic ulcer seen at the Mayo Clinic in the decade preceding Jan. 1, 1945. Of these 93 were operated upon, 3 being moribund on admission. There were 11 post-operative deaths.

Spinal anesthesia appears to be the anesthesia of choice for simple closure, while the combination of light general anesthesia and curare intravenously to secure muscular relaxation has great promise. The incision should be kept small because of the high incidence of wound infection. The operation should be limited to closure of the perforation in almost all cases of perforated duodenal ulcer. Some cases of perforated gastric ulcer may require subtotal gastric resection because of a questionable malignancy.

FRANK G. VAL DEZ.

DRIVER, R. L. Comparative efficacy of pancreatin and pepsin in the experimental production of intestinal ulcers. *Arch. Path.*, 40: 34 (July) 1945.

Intestinal loops about 18 inches long, extending from the mid-duodenum to a point in the jejunum 12 inches below the muscle of Treitz, were studied in 107 anesthetized dogs. The object was to show the influence of pressure in the production of intestinal ulcers when the loops were exposed to various solutions.

In the absence of pressure there was no damage noted in the intestinal loops when they were exposed to N/10 sodium bicarbonate, to 0.1% pancreatin in N/10 sodium bicarbonate, and to 0.1% pepsin in N/10 sodium bicarbonate. There was minimal damage seen (0.5 on a scale of 1 to 4) when N/10 hydrochloric acid alone and when a solution of 0.1% pancreatin in N/10 hydrochloric acid were used; and damage, graded 1.9, was noted when a solution of 0.1% pepsin in N/10 hydrochloric acid was likewise used. However, under a pressure of 90 cm. of water, there was present grade 4 damage in the loops when N/10 hydrochloric acid was used alone and also when solutions of 0.1% pancreatin, and 0.1% pepsin in N/10 hydrochloric acid were employed. There was 1.8 grade damage when 0.1% pancreatin in N/10 sodium bicarbonate was used, and no damage from N/10 sodium bicarbonate alone or when 0.1% pepsin was added to it. The conclusions drawn were that pancreatin in N/10 sodium bicarbonate produces ulcers in the intestine of dogs in 10 hours under the hydrostatic pressure of 90 cm. of water, but no damage in the absence of the intra-intestinal pressure. The ulcer producing effect of N/10 hydrochloric acid and 0.1% pancreatin was due to the hydrochloric acid and not to the pancreatin. Pepsin in N/10 sodium bicarbonate produces no ulcers with or without pressure.

N. W. JONES.

RANSOM, H. K. Gastrojejunocolic fistula. *Surgery*, 18: 177 (Aug.) 1945.

The author states that of 47 patients with marginal or jejunal ulcers, treated surgically over a 10-year period, 8 (17%) of the surgical cases had the complication of gastrojejunocolic fistula. Over a 20 year period, 18 cases of gastrojejunocolic fistula were observed and 14 of these were treated by operation. Seventeen of these 18 cases were in men, and all followed a previous posterior gastroenterostomy for a duodenal ulcer. The interval between the original operation and the admission for treatment of the fistula was less than 2 years in 2 cases, but the longest interval was 26 years. In only one of 15 cases in which the exact site

of the fistula could be determined was there a true jejunocolic fistula. The other cases were either gastrojejunocolic fistulas or developed from jejunal ulcers so close to the stomach as to be, for all purposes, truly gastrojejunocolic. The size of the fistulous openings varied considerably, ranging from 0.5 cm. to 6 cm. in diameter.

The development of gastrojejunocolic fistula may be characterized by a recurrence of ulcer symptoms due to a recurrent marginal or jejunal ulcer. One-third of the 18 cases had pain. In the others there was no pain prior to the development of symptoms of fistula. The characteristic symptoms included severe diarrhea, often with the passage of undigested food, vomiting, which is often feculent, and pronounced weight loss. Of the laboratory findings, anemia, hypoproteinemia and decrease in the prothrombin were most important. X-ray is of course most valuable in arriving at a diagnosis, and if established the correct diagnosis in 15 of 17 cases. The barium enema is most helpful. The preoperative preparation of the patient, to correct hypoproteinemia and hypoprothrombinemia and restore electrolyte balance, is also good. In the 18 cases treated, different types of operations were performed, including restoration of continuity with triple closure, and various combinations of gastric and jejunal resections with colonic closures. Of 14 patients operated on, two died, a mortality of 14.3%.

The end results were good in 4 cases of 9 in which gastric resection was not done at operation, and in all 3 patients who had gastric resection and survived operation. Ransom, therefore, felt that gastric resection offers the best hope for permanent cure, but since these patients are often poor risks, it often cannot be done and must be postponed for a later occasion if need for it arises. This paper also includes mention of gastroenteric fistulas resulting from tuberculosis and carcinoma. In only 1 of 6 such cases was surgical correction attempted, and a block resection was done.

HENRY TUMEN.

PROCTOLOGY

PRATT, J. H. AND JACKMAN, R. J. Perforations of the rectal wall by enema tips. *Proc. Staff Meet. Mayo Clinic*, 20: 277 (Aug.) 1945.

Perforation of the rectal wall by an enema tip fortunately is encountered but rarely as a surgical emergency. Twenty cases of actual perforation are reported from the literature. Such accidents occurred mainly in two groups of people: pregnant women at term, and elderly individuals. The actual incidence of perforation of the rectum by an enema nozzle is not known, but undoubtedly many cases have not been reported and perhaps not even recognized. The bowel wall is not only perforated but the irritating enema solution is introduced either into the peritoneal cavity or behind the rectal wall. Even partial perforation through the bowel wall, with injection of the irritating material beneath the mucosa or the muscularis, results in large sloughs with consequent infection, stricture, and even death. Injection of the enema material into the free peritoneal cavity results in the onset of a typical acute peritonitis. Immediate laparotomy should be performed with closure of the defect, and 10 to 15 g. of sulfathiazole should be left in the abdomen. Two cases of rectal perforation in elderly individuals are presented. One of these suffered an acute perforation which was proctoscoped, and a catheter inserted into the defect as a landmark and subjected to immediate operation. The second person had had a perforation three months previously, with the development of peritonitis and a pelvic mass. At operation, a constricting mass was found about the sigmoid and a proximal colostomy was performed. The colostomy was closed five and one half months later when the inflammatory mass had regressed. The authors emphasize that an enema tip need not and should not be inserted further than 5 cm. into the rectum.

FRANK NEUWELT.

SMITH, N. D. Considerations in surgical treatment of several common anorectal abnormalities. *Surg. Clinics N. Am.*, 969(Aug.) 1945

Reasonable frankness is encouraged in discussing the operation with the patient concerning anticipated discomfort of ano-rectal surgery. Sacral or low spinal anesthesia proves most satisfactory. All of the operations are designed to permit ample drainage because of the inability to produce or maintain a sterile field postoperatively. The simplest example of a desirable sort of anal wound is given by the classical method for drainage of an infected crypt. The relationship of skin and mucous membrane is not appreciably altered and the wound is not sutured closed. Muscle fibers are not incised and they form the base of the wound. Sutures are placed at the dentate margin. A similar application of these principles to the surgery of anal fissure, external and internal hemorrhoids, and fistula in ano, is discussed.

FRANK G. VAL DEZ.

BODKIN, L. G. Oral therapy for pruritus ani. *Am. J. Dig. Dis.*, 12: 255 (Aug.) 1945.

This author made a survey of 42 personal cases of pruritus ani, treated with oral medication and local application. A formula containing Takadiastase and Sodium Dilatin was considered an effective combination. Locally, soap and water was avoided. Silver nitrate was applied to existing local fissures and to those within the anal canal. Alcohol, mineral oil, condiments, and fried foods were omitted entirely.

H. J. SIMS.

SURGERY

SMITH, B. C. Experiences with the Miller-Abbott tube. A statistical study of 1000 cases. *Ann. Surg.*, 122: 253 (Aug.) 1945.

This is a statistical review of the use of the Miller-Abbott tube in 1,000 patients at the Presbyterian Hospital, New York City. The tube's chief function on the surgical service is deflation of the small intestine. Preoperatively, it has served to decrease the incidence and severity of ileus, to diagnose the presence and site of small intestinal tumors, foreign bodies, adhesions, kinks, bands, and malformations (using a small amount of barium through the tube when

needed). At operation, it has served as a guide to the site of obstruction and permitted the small intestine to be removed from the operative area by pleating on the tube. Postoperatively, it has given continuing intestinal deflation, thereby aiding circulation to the bowel and permitting better peristalsis and absorption. It has made possible the enteral administration of fluids, electrolytes, glucose, proteins and medication.

The author gives detailed data on these experiences in 24 tables. One significant note is that intubation failed, i.e., the tube did not pass the pylorus, in 220 patients or more than a fifth of those on whom it was used.

LEMUEL C. MCGEE.

KOZOLL, D. D., HOFFMAN, W. S. AND MEYER, K. A. Nitrogen balance studies on surgical patients receiving amino acids. *Arch. Surg.*, 51: 59 (July-Aug.) 1945.

Parenteral injections of amino acids were used as the only source of protein during a study of nitrogen balance in 14 cases of obstructing lesions of the esophagus or stomach. Positive nitrogen balance was achieved in 13 cases.

The quantity of amino acids required by parenteral injection for positive nitrogen balance varied between 60 and 90 g. per day. At times, doses of 120 g. were used to produce larger positive balances. The serum protein concentration rose during treatment in 4 cases, remained stationary in 2, and fell in 8. The serum albumin concentration rose in 6 cases and declined in 8.

Therapy with parenteral injections of amino acid should be accompanied with an effort to meet carbohydrate, mineral, and vitamin requirements. A minimal daily carbohydrate intake of 300 g. is required.

In clinical practice (1) oral, intragastric or transgastric feedings of protein or amino acids, and (2) transfusion of whole blood are recommended in addition to parenteral injections of amino acids.

FRANCIS D. MURPHY.

PETERSON, L. W. AND COLE, W. H. Chronic sclerosing pancreatitis causing

complete stenosis of the common bile duct. *Arch. Surg.*, 51: 15 (July-Aug.) 1945.

Operative therapy is directed at establishing a permanent, non-stenosing communication between the suprapancreatic portion of the common bile duct and the intestinal tract. Regurgitation of food and intestinal secretions into the duct must be prevented if possible.

The procedure of choice is an anastomosis of the proximal stump of common duct to the duodenum, or the anastomosis of the proximal end of the common bile duct to the blind end of a single arm of jejunum, utilizing the Roux principle. Into this blind loop of jejunum, through which food does not ordinarily pass, valves are placed to act as baffles to help prevent regurgitation of food. A side to side anastomosis has the added advantage of allowing function of the terminal duct to be resumed if the pancreatic lesion clears sufficiently to allow relief of the obstruction. If the terminal end of the duct is hopelessly destroyed, the duct may be mobilized and either a transplantation into the duodenum or an anastomosis performed.

The postoperative course in the 3 cases presented has been satisfactory. None has had recurrence of jaundice or chills, which would be expected if a stricture reformed or cholangitis developed.

FRANCIS D. MURPHY.

COUNSELLER, V. S. Surgery of the stomach and duodenum. *Surg. Clinics N. Am.*, 891 (Aug.) 1945.

Only about 15-20% of the patients with duodenal ulcer require surgical intervention, and these consist of carefully selected cases who have not responded to medical therapy or who have repeated and massive hemorrhage, obstruction, or perforation. In the presence of associated diseases such as gall stones, a cholecystectomy may be desirable, but the guide should be the surgeon's ability, and the limitation of multiple surgical procedures.

In the case of gastric ulcer, the management must be less conservative. The percent operated upon for gastric ulcer varies between 40-60%. All gastric ulcers

should be regarded as malignant until proven benign. The location, size, and response to medical management are all factors in deciding surgical intervention.

Carcinoma of the stomach requires early diagnosis for adequate resection. Physical and roentgenologic examination alone will not always disclose the resectability of the lesion, and where doubt exists, exploratory laparotomy should be performed.

FRANK G. VAL DEZ.

WAUGH, J. M. AND FAHLUND, G. T. R. Total gastrectomy. *Surg. Clinics N. Am.*, 903 (Aug.) 1945.

Seventy-seven cases of total gastrectomy, performed at the Mayo Clinic since 1917, are reviewed in detail. The over-all mortality was 44.2%. From 1917 to 1929 the mortality was 60.6%, while from 1940 to 1943 (44 cases) the mortality rate was 31.8%; in 1943 (20 cases) it was only 25%. Sixty-seven of the cases were done for carcinoma, 7 cases for benign lesions, and 3 for lymphosarcoma.

Bronchopneumonia was the most frequent post-operative complication (23 cases). Only 6 patients succumbed with bronchopneumonia as the chief cause of death. Prophylaxis and early treatment of pulmonary atelectasis tended to diminish the incidence of pneumonia. Peritonitis was the most common cause of death (21 cases or 61.8%), in most cases due to a leakage at the line of anastomosis. Cardiac failure and impending shock were the other most frequent complications. More than half of those patients who survived the operation of total gastrectomy for cancer lived 2 or more years. Two patients who underwent the operation for benign lesions have lived six and eight years respectively, and are still alive as of Feb. 1., 1944.

FRANK G. VAL DEZ.

BACON, H. E. Evolution of sphincter muscle preservation and re-establishment of continuity in the operative treatment of rectal and sigmoidal cancer. *Surg. Gyn. Obs.*, 81: 113 (Aug.) 1945.

The evolution of surgical extirpation for rectal and low sigmoidal cancer, designed to eliminate the establishment of an ab-

dominal colostomy, is discussed. Preservation of the sphincter muscles does not augment operative mortality. In over 80% of cases, the sphincter musculature may be preserved, and evidently, it does not affect the survival rate. From 712 cases of radical resection without colostomy, 208 personal extirpations of the rectum and sigmoid for carcinoma were selected for discussion, and an attempt was made to evaluate and compare this series with other precedures.

The Babcock abdominoperineal technique of proctosigmoidectomy without colostomy and with preservation of the sphincter muscle possesses merit. It permits radical removal of the malignant bowel and gland-bearing areas, and, in spite of a high rate of resectability, enjoys a low operative mortality. It also allows early discharge of the patient, reduces the period of wound healing, and affords early return to work. Improvements and refinements in technique, such as the establishment of an anterolateral pelvic diaphragm, prevent descent of the small bowel into the perineal wound. Precise maintenance of essential blood supply avoids retraction and necrosis, and preservation of the sphincter musculature offers varying degrees of continence.

FRANCIS D. MURPHY.

MONTEIRO, A. Aseptic gastric resection.

Surg. Gyn. Obs., 81: 177 (Aug.) 1945.

The author describes a technique to avoid opening the stomach and intestinal cavities at the time of anastomosis. Briefly stated, it is as follows: (1) With a special forceps the portions of the stomach and intestine where the anastomotic opening is to be made are crushed. This crushing traumatizes particularly the mucosa and muscularis, and has the least effect on the serosa. (2) Caustic potash is applied to that portion of the gastric and intestinal serosa demarcated by the blades of the forceps. (3) A seromuscular suture is made around the crushed and causticized area. After 48 hours, when this tissue sphacelates, the anastomotic opening is sealed off without contamination by coalescence of the serosas held in apposition by the sutures.

The technique of aseptic gastrectomy has

been used in 40 cases of ulcer with 1 death; this death was not the result of faulty technique. With this technique it is possible to avoid filiform drainage along the sutures from the mucosa. This drainage, with contamination, is inevitable if the sutures run through all layers of the stomach or bowel.

FRANCIS D. MURPHY.

SHIER, R. V. B. Right colon resection.

Can. Med. Assoc. J., 53: 18 (July) 1945.

End-to-end anastomosis of the ascending colon is superior to the side-to-side variety, in that no elongated blind pocket is left for stagnation of feces. The operation is successful provided there is adequate pre-operative preparation, good exposure at operation, careful preservation of blood supply, and rigid surgical technique.

IRVING WOLMAN.

PHYSIOLOGY: MOTILITY

ARENDT, J. The significance of Cannon's point in the normal and abnormal function of the colon. Am. J. Roent. Rad. Therapy, 54: 149 (Aug.) 1945.

In studying the physiologic function of the colon it may sometimes be noted that the ascending and first part of the transverse colon are contracted, while the second part and the descending colon are of normal diameter; in other cases, however, the reverse may be observed. At the point where this change takes place, a division or a contraction ring is frequently seen, usually occurring on the right side or middle-third of the transverse colon. The earliest observation of this phenomenon was made by Cannon, and it has since been frequently reported by others.

In discussing the etiology of this contraction, it is noteworthy that there is no hypertrophy of muscle fiber and no accumulation of ganglion cells suggestive of a sphincter. The author's explanation, based upon roentgen observations, is that it is the pivoting point of a change in nerve innervation between the vagus and pelvics and between the superior and inferior splanchnics. The author's roentgenologic observation is also

supported by embryologic findings. The point of transition of the extrinsic nerve impulses is designated Cannon's point. To be visible in roentgenograms, an antagonism between both neurological units is necessary.

MAURICE FELDMAN.

METABOLISM AND NUTRITION

CAYER, D., RUFFIN, J. M., AND PERLZWEIG, W. A. Vitamin levels in sprue. *Am. J. Med. Sci.*, 210: 200 (Aug.) 1945.

In 12 patients with clinical manifestations of sprue the following laboratory tests were applied: plasma ascorbic acid; vitamin A and carotene; urine content of B-complex vitamins after test doses of thiamin, riboflavin, nicotinic acid amide, and pyridoxine. Comparisons were made with a control group of 30 medical students, and a group of 25 patients showing evidence of a mild deficiency of the B-complex vitamins.

The mean values from the analyses on sprue patients were lower than the suggested minimal normal levels, except in the value for pyridoxine. The striking difference between the sprue patients and the patients showing a B-complex deficiency was found in plasma vitamin A and carotene levels. The average value for carotene in sprue patients was 49 I.U., and in B-complex deficient patients, 205 I.U. The authors conclude that plasma vitamin A and carotene determinations are helpful in the diagnosis of sprue.

LEMUEL C. MCGEE.

ANATOMY

NEUHOF, H. AND BLOOMFIELD, S. The surgical significance of an anomalous cholecystohepatic duct—case reports. *Ann. Surg.*, 122: 260 (Aug.) 1945.

Two cases are reported wherein an accessory hepatic duct, draining a segment of the liver, emptied directly into the gall bladder. This biliary pathway is called an anomalous cholecystohepatic duct. Such a duct is said to occur regularly in fish, reptiles, and birds. Its incidence in man is unknown.

Inasmuch as such an accessory duct is

inevitably severed during cholecystectomy, failure to recognize it leads to bile leakage, and possibly infection with peritonitis. In one of the two patients described in this report, the anomalous duct was left open for external drainage; in the other patient it was ligated. The latter procedure is recommended as the preferred one, unless there is known to be infection in the liver segment which the duct drains.

LEMUEL C. MCGEE.

MISCELLANEOUS

FRADKIN, W. Z. The diarrhea problem. *Am. J. Dig. Dis.*, 12: 261 (Aug.) 1945.

A table showing mortality from diarrheal diseases in the U. S. from 1927 to 1940, which represented a total of 377,507 deaths, was presented. This indicated an average annual mortality rate of 26,965. The author's conclusions are: (1) Diarrhea is an urgent laboratory problem. (2) It is one of vital nutrition control. (3) It requires segregation, hospital service with a specialized team, and a specialized group of clinicians cooperating. (4) Diarrhea must be checked promptly in order to avoid serious social, medical, and surgical complications. A diarrheal disease is considered a menace and potent danger to public health, and systematic study of the disease will lead to further progress in this field.

H. J. SIMS.

FRADKIN, W. Z. General treatment of diarrheal diseases. *Am. J. Dig. Dis.*, 12: 263 (Aug.) 1945.

This clinician outlined a supportive treatment for diarrheal patients. The diagnostic features, when associated with deficiencies in vitamin A, thiamin chloride, riboflavin, nicotinic acid amide, and ascorbic acid, were outlined. The appropriate treatment relating to each deficiency was discussed.

H. J. SIMS.

LOGAN, G. B. Acute nonsurgical emergencies related to the gastro-intestinal tract. *Med. Clinics N. Am.*, 878 (July) 1945.

This paper is concerned with gastrointestinal

disease in infants and children. Logan deals with colic, warning that all crying doesn't mean pain, since air-swallowing, food idiosyncrasy, and fatigue are also causes of colic. Appendicitis may be present without nausea, vomiting, diarrhea or fever. Tenderness at McBurney's point, rebound tenderness, and rectal tenderness on the right are important. Pneumonia with abdominal pain is mentioned. In-

tussusception is surgical and urgent. Henoch's purpura is discussed, especially as to treatment. Lead poisoning is considered as to etiology and treatment. The acute diarrheas are important. Elimination of a possible surgical condition should be done first. The possibility of dehydration must be in mind, to prepare for parenteral fluids if necessary. Taking of poisons by children is dealt with briefly.

MILLS STURTEVANT.

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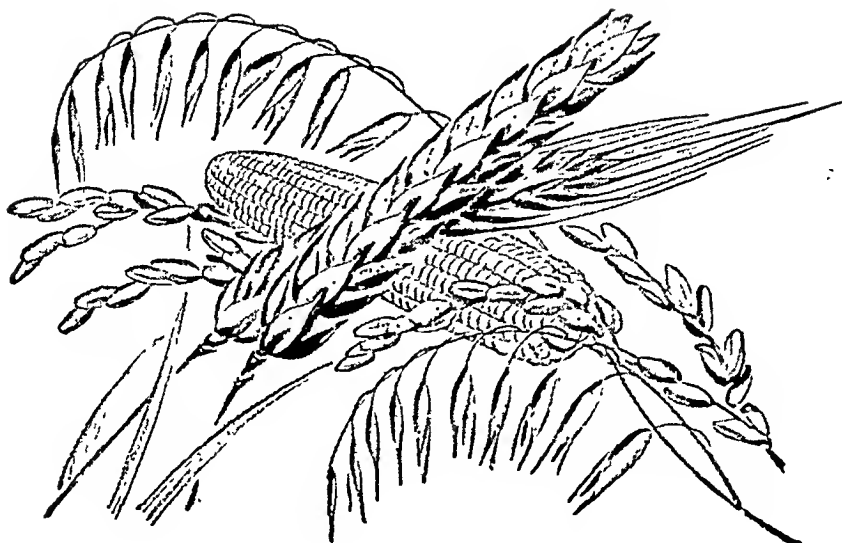
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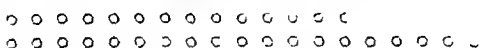
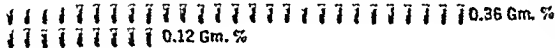
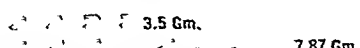
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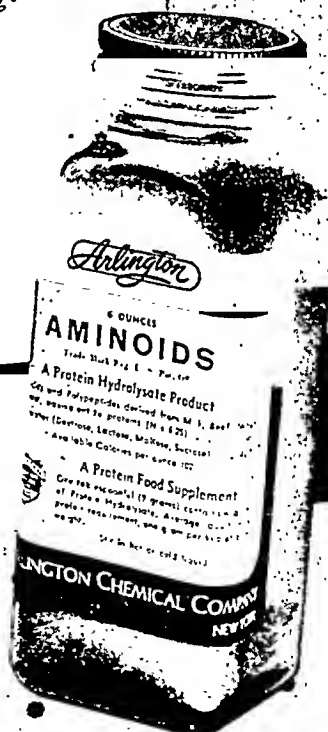


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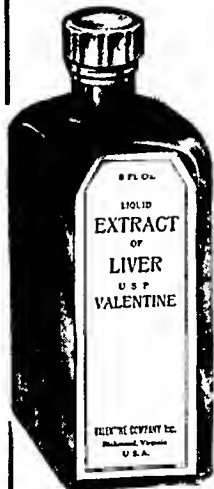
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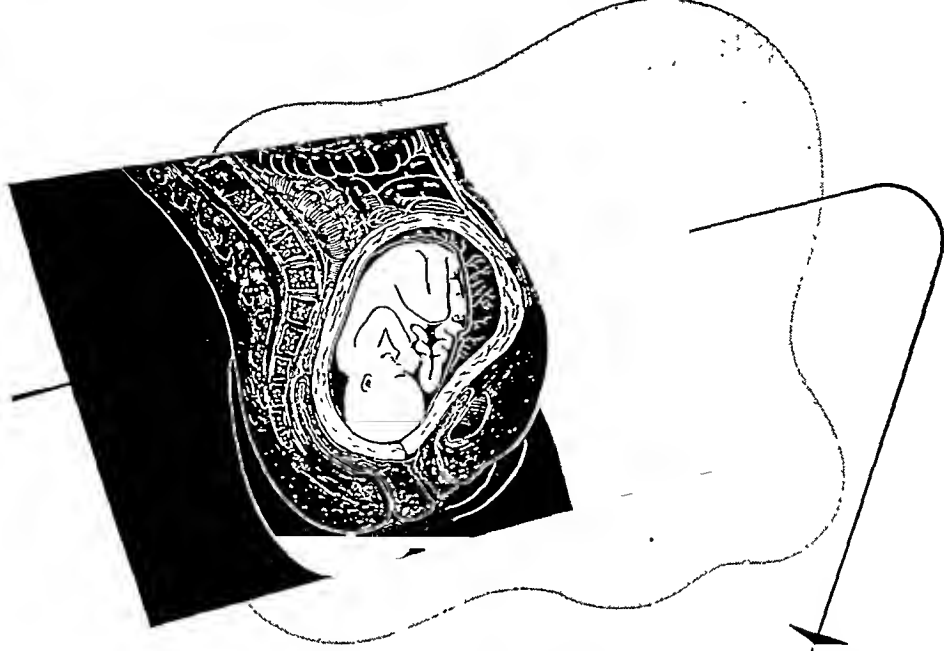
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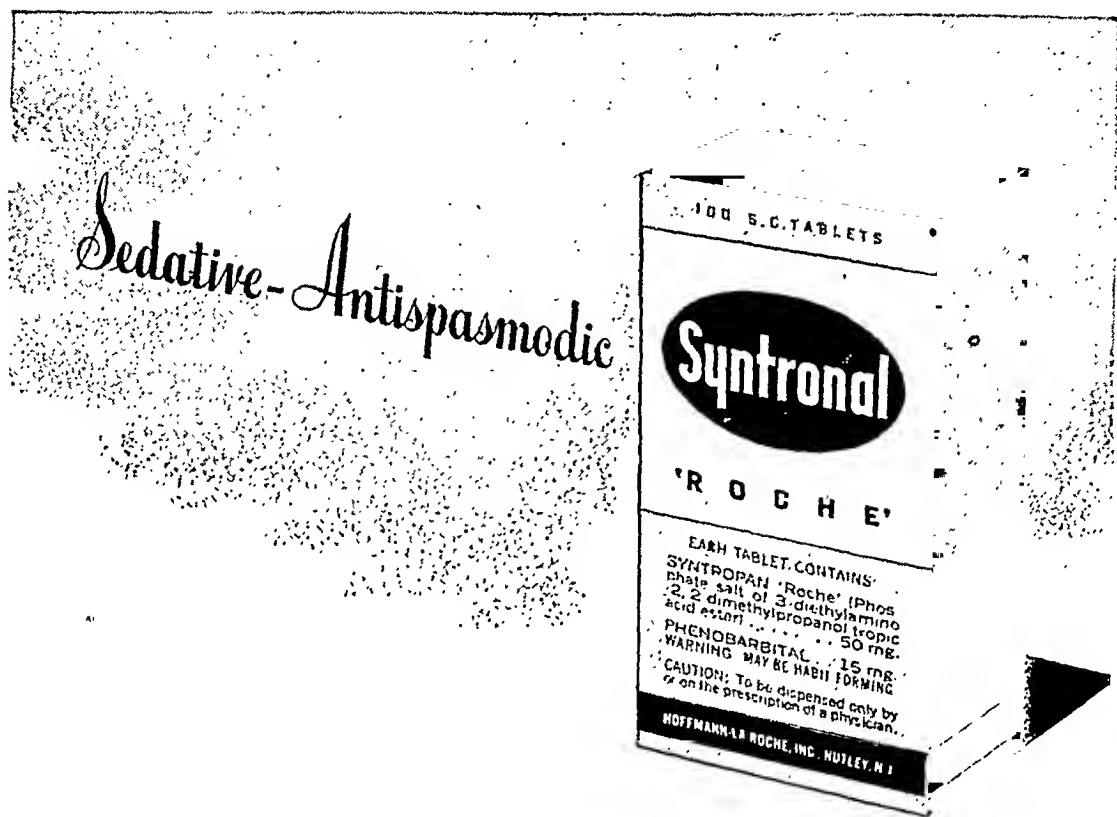
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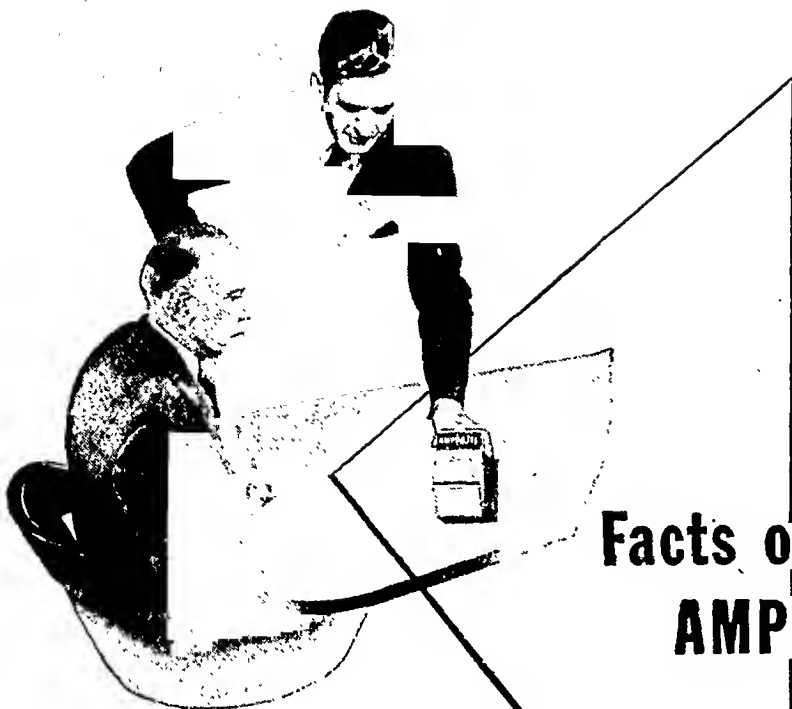


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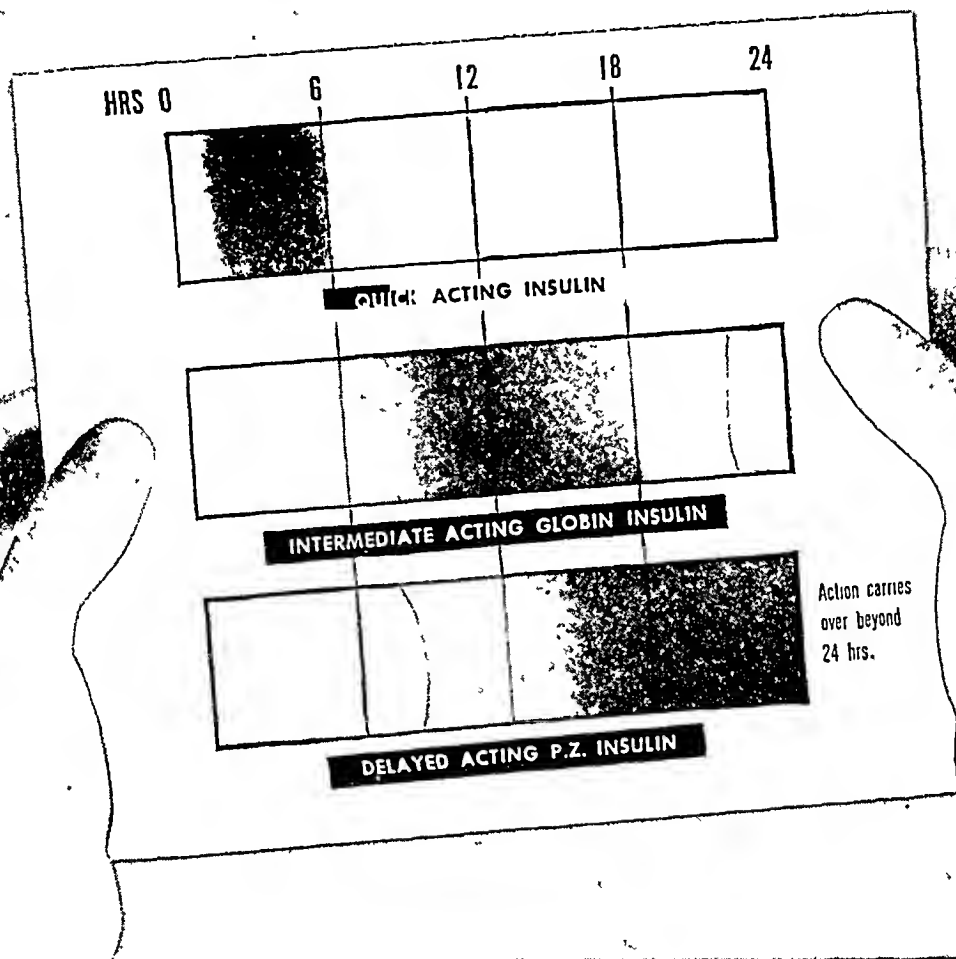
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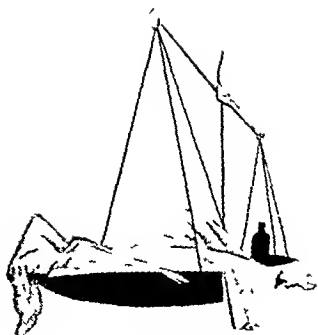
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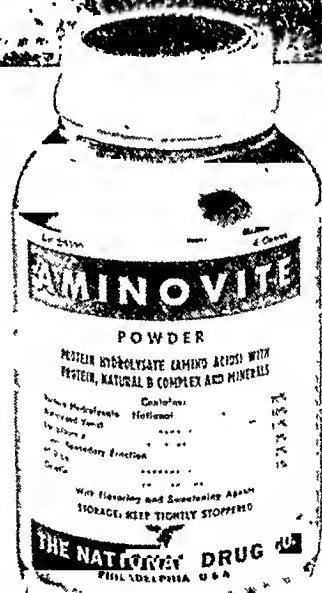
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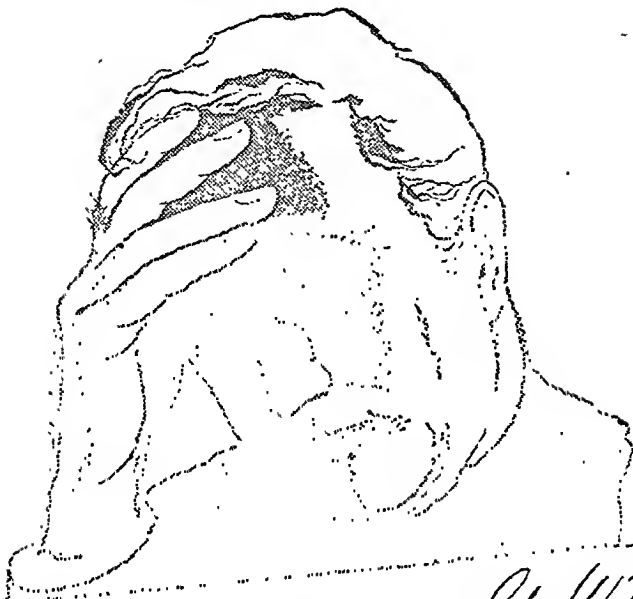
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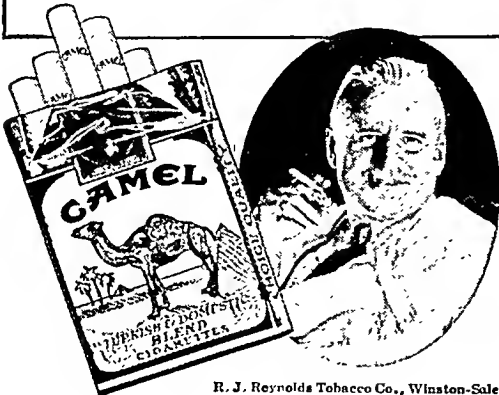
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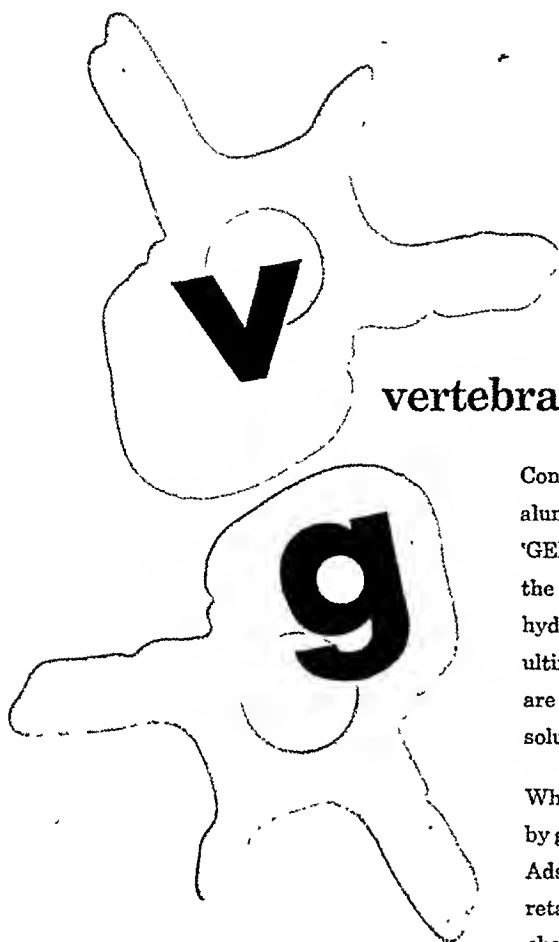


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GASTROENTEROLOGY

Official Journal of the American Gastroenterological Association

VOLUME 6

JUNE 1948

NUMBER 6

THE INCIDENCE OF GASTROINTESTINAL DISORDERS

FROM A STUDY OF 2,839 CASES

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INTRODUCTION

A knowledge of the incidence of disease serves as a guide to the physician in making a diagnosis and, perhaps more important, acts as a challenge to his general diagnostic ability.

Unfortunately, it is difficult to obtain reliable statistics on the morbidity of disease. The accuracy of figures taken from departments of public health and insurance tables is limited by the varying skill and accuracy of the reporting physicians. Figures reported from large clinics are influenced by the type of patient which is seen. For example, the mortality from bleeding ulcer is reported from 3 to 20 per cent, depending upon whether the figures have been derived from private practice or from large metropolitan clinics which may care for irresponsible, indigent individuals. Moreover, figures change with the development of new diagnostic methods and under the influence of new ideas. In the field of gastroenterology the x-ray has both simplified and increased the accurate recognition of organic lesions. At the same time, the developing interest in psychosomatic medicine has emphasized the importance of functional disorders. Therefore, it is desirable from time to time, to re-evaluate the relative incidence of disease.

The present paper reports the incidence of gastrointestinal disorders as encountered in a relatively large city. An ideal investigation should include a broad sampling of the community, running into thousands of cases and should be drawn from material which has received intensive study by modern methods. However, it is practically impossible to achieve such an ideal. The medical trend toward specialization or, at least, toward a limited practice has advanced to such an extent that a large proportion of physicians are not caring for a general practice in the old sense of the term. Similar objections exist when such a study is made from the files of a large metropolitan hospital. To increase efficiency, our general hospitals divide their activities in such a

way that, no one, from the physician-in-chief to the newest intern, comes in contact with the same diversity of conditions as does the general practitioner. However, the hospital files should have some advantages over those of private records. Hospital patients probably receive more complete study because of the convenient laboratory facilities.

THE MATERIAL

Realizing the limitations necessarily inherent in any statistical survey of this kind, I have studied the following material as seemingly the best way of obtaining the desired data:

1. The records of 1000 consecutive patients of the Outdoor Department of the Peter Bent Brigham Hospital.
2. The records of 1000 ward patients, 500 medical and 500 surgical. So far as possible, these were in consecutive order.
3. The incidence of various organic diseases of the gastrointestinal tract recognizable by the x-ray.
4. The records of 839 patients of a physician's private practice.
5. 500 consecutive autopsy protocols at the Peter Bent Brigham Hospital.

Outpatient records should give a better concept than ward records of the frequency of gastrointestinal complaints relative to all those which lead individuals to seek medical advice. The patients having minor surgical and medical ailments do not ordinarily enter the wards. Also, a patient who is thought to be suffering from a functional ailment is not usually sent into the wards. The outpatients at the Peter Bent Brigham Hospital come from a diverse group in the community. Some are referred by outside physicians. Many come on their own initiative and for various reasons—some for financial reasons—some because they have no family physician—some because a friend recommended the hospital—some because they have failed to obtain relief elsewhere. The last group includes many functional patients who are constantly shopping around. These outpatient cases represent a wide range of occupations and social standings. All sorts of manual laborers and white-collar workers are seen. Although the greater number of entrants are indigent, there are many who are definitely not poverty-stricken. Most of the patients live nearby, but a few wander in from more distant places, occasionally from outside the State. This group doubtless represents a fair sampling of those diseases which exist in and around a city like Boston. For the study of these patients, the facilities of all the hospital diagnostic procedures are employed.

I was fortunate in receiving permission to study the records from a physician's private practice. This practice includes many instances of family care, together with a certain number of patients seen only in the office. The

physician is a highly trained individual having a broad range of medical interests. This sample provides a wide group of patients treated by a physician conversant with and able to use the modern diagnostic procedures. Eight hundred and thirty-nine records were consulted in this sample.

INCIDENCE OF GASTROINTESTINAL DISORDERS

Table 1 shows that approximately 17 per cent of the Outdoor cases, 23 per cent of the ward cases and 16 per cent of the private cases were seen because of a gastrointestinal disorder. This is an average of 19.1 per cent. In other

TABLE 1

The relative involvement of the various bodily systems as obtained in a study of 1000 consecutive out-patient records, of 500 surgical and 500 medical admissions to the wards of the Peter Bent Brigham Hospital, and 839 cases from a private practice

PER CENT OF:	FBBH OUTPATIENT	FBBH WARD	PRIVATE PRACTICE
	% Cases	% Cases	% Cases
Gastrointestinal patients.....	17.5	23.3	16.5
Cardiovascular.....	10.4	13.7	8.4
Genito-urinary.....	10.0	12.6	6.2
Bones and joints.....	7.0	3.0	10.1
Respiratory.....	6.4	12.2	21.2
Skin.....	6.0	3.7	2.1
Nervous.....	2.2	14.1	10.8
Metabolic.....	1.9	4.5	2.9
Blood.....	1.0	2.6	1.2
Trauma (including hernia).....	16.7	7.3	0.8
Infection.....	11.6	0.3	0.2
Headache.....	3.2	0.1	2.6
No disease.....	6.1	0.9	14.6
Syphilis.....		0.5	
Acute poisoning.....		0.5	
Tumors.....		0.2	0.1
Eyes, ears, nose, teeth.....			1.7

words, approximately one-fifth of the total 2839 patients in this study applied for treatment of their gastrointestinal tract.

Some variations exist between the figures obtained from the three samples. Trauma and infection are more numerous in the outdoor department than in the wards or private practice because most of these disorders were not serious enough for hospitalization. The smaller incidence of these disorders on the wards automatically increases the percentage of other disturbances. However, the strikingly greater percentage of nervous disorders on the wards is due to the large number of patients admitted to the service of the late Dr.

Harvey Cushing. The larger number of cardiovascular disorders seen on the wards comes from the number of patients incapacitated by the arteriosclerotic changes coincident with age. The genito-urinary cases included the complications of pregnancy such as miscarriages which are usually referred directly to the wards. The greater number of respiratory disorders are in part due to the pneumonias and in part to the hospitalization of the nurses and resident staff for acute respiratory infections.

Cases classed as respiratory disorders and as "no disease" were encountered more often in private practice than in the hospital. Upper respiratory infections severe enough to keep a person indoors but too mild for admission to the wards explains this difference. The larger number of private patients classed as "no disease" are made up of those individuals who merely wished a physical examination or who came in for preventive medicine such as inoculations against typhoid.

In general, the various bodily systems are involved in about the following order: gastrointestinal, respiratory, cardiovascular, genito-urinary, nervous system, bones and joints, skin, diseases of metabolism and finally, the blood.

The criteria for establishing a diagnosis of organic or non-organic disease need classification, as will be discussed later on. For this reason the ratio of organic to non-organic disease is difficult to determine accurately. However, for the purpose of this paper the criteria used for classifying a disease as organic consist of the following: Those conditions which were recognized by the x-ray, by direct visualization through a gastroscope or sigmoidoscope, by operation or by autopsy. Cases of infectious gastroenteritis were also included. All such cases were associated with food poisoning or an acute respiratory infection and all ran a fever.

Table 2 shows that organic disease was encountered in 46.2 per cent of the outdoor patients; 89.5 of the ward patients and 40.4 per cent of the private patients. This leaves as functional, 53.8 per cent for the outdoor department; 10.5 per cent for the wards and 59.6 per cent for the private patients.

The relative incidence of organic diseases as encountered in this study is portrayed in tables 3, 4, and 5.

Table 3 reveals the organic diseases recognized in the outdoor department, the wards and in the private practice. It includes the percentage of each disease to the number of organic diseases recognized in each sample and to the total number of patients in each sample. Certain differences between the figures recorded in the outdoor department and wards can be easily explained. Gallbladder disease exceeds peptic ulcer on the wards; whereas, the reverse is true of both the outdoor department and private practice. This is because a greater proportion of gallbladder cases will be referred to the wards for treatment than ulcer cases, many of whom will be treated while ambulatory.

The failure to record any cases of carcinoma and diverticulosis in the outdoor department is disturbing, as 7-10 of these should have been seen in view of the

TABLE 2

The relative incidence of organic and functional disorders as recorded in the hospital records of the outpatient department, wards and in a private practice

	OUTPATIENT DEPARTMENT		WARDS		PRIVATE PRACTICE	
	No.	%	No.	%	No.	%
Organic.....	81	46.2	205	89.5	83	40.4
Functional.....	94	53.8	24	10.5	122	59.6
Total.....	175	100	229	100	205	100

TABLE 3

The type and frequency of the various intestinal disorders diagnosed in the outpatient department and wards of the Peter Bent Brigham Hospital and in the records of one individual's private practice. The percentages are relative to the number of organic disorders and the number of cases in each sample

	OUTPATIENT DEPARTMENT			WARDS			PRIVATE PRACTICE		
	No.	% organic cases	% total cases	No.	% organic cases	% total cases	No.	% organic cases	% total cases
Ulcer.....	29	35.8	2.9	40	19.5	4.0	15	18.0	1.8
Gallbladder.....	16	19.7	1.6	44	21.4	4.4	7	8.4	0.8
Appendicitis.....	16	19.7	1.6	32	15.6	3.2	3	3.6	0.3
Carcinoma.....	0	0	0	24	11.7	2.4	8	9.6	0.9
Diverticulosis.....	0	0	0	10	4.7	1.0	5	6.0	0.6
Hemorrhoids.....	9	11.1	0.9	17	8.2	1.7	8	9.6	0.9
Gastroenteritis.....	4	4.9	0.4	7	3.4	0.7	25	30.1	2.9
Diaphragmatic hernia.....	0	0	0	4	1.9	0.4	3	3.6	0.3
Catarrhal jaundice.....	1	1.1	0.1	6	2.9	0.6	3	3.6	0.3
Hepatic cirrhosis.....	1	1.1	0.1	5	2.4	0.5	1	1.2	0.1
Acute yellow atrophy.....	0	0	0	0	0	0	1	1.2	0.1
Ischi-rectal abscess.....	0	0	0	0	0	0	1	1.2	0.1
Fistula in ano.....	3	3.3	0.3	2	.9	0.2	0	0	0
Congenital anomaly.....	0	0	0	0	0	0	1	1.2	0.1
Echinococcus cyst.....	0	0	0	0	0	0	1	1.2	0.1
Gastrointest. hem.....	0	0	0	0	0	0	1	1.2	0.1
Parasites.....	0	0	0	4	1.9	0.4	0	0	0
Ulcerative colitis.....	0	0	0	3	1.4	0.3	0	0	0
Benign tumors.....	1	1.1	0.1	2	.9	0.2	0	0	0
Perianal abscess.....	1	1.1	0.1	1	.4	0.1	0	0	0
Torsion omentum.....	0	0	0	1	.4	0.1	0	0	0
Postoperative trouble.....	0	0	0	3	1.4	0.3	0	0	0
Total.....	81	98.9	8.1	205	99.0	20.5	83	99.7	9.4

incidence obtained from the other two samples. It raises the question of whether there were no cases of this kind in the relatively small sample, or

TABLE 4

The incidence of organic diseases as recognized in the X-ray Department of the Peter Bent Brigham Hospital

	NO. CASES	PERCENTAGE
Peptic ulcer.....	605	35.6
Duodenal.....	479	28.2
Gastric.....	105	6.19
Pyloric.....	16	0.94
Hour-glass stomach.....	3	0.17
Esophagus.....	2	0.11
Carcinoma.....	458	26.9
Stomach.....	221	13.0
Colon.....	140	8.24
Esophagus.....	43	2.54
Rectum.....	37	2.18
Pancreas.....	8	0.47
Gallbladder.....	5	0.29
Duodenum.....	2	0.11
Mouth.....	2	0.11
Inflammation of gallbladder.....	288	16.8
Cholelithiasis.....	206	12.02
Without stones.....	82	4.82
Diverticulosis.....	181	11.6
Diverticulosis of colon.....	76	4.47
Diverticulosis of duodenum.....	40	2.36
Diverticulitis of colon.....	34	2.02
Esophagus.....	23	2.32
Stomach.....	8	0.47
Diaphragmatic hernia.....	70	4.12
Ulcerative colitis.....	30	1.76
Gastritis.....	20	1.17
Cardiospasm.....	15	0.88
Cicatrizing enteritis.....	13	0.76
Benign tumors.....	7	0.41
Foreign body.....	7	0.41
Megacolon.....	2	0.11
Esophageal fibrosis.....	2	0.11
Total.....	1698	100.78

TABLE 5

Shows the distribution of histological lesions found in the digestive organs of 500 autopsied cases

No. of cases.....	197	147	89	55	8	3	1
No. of lesions.....	0	1	2	3	4	5	6

whether they were missed and classed as functional. There is a much higher incidence of acute gastroenteritis recorded among the private group. The incidence of hemorrhoids is about the same in all groups. These figures indicate only the number of cases that sought medical advice or treatment for the condition. The incidence of parasites will vary with the geographical location from which the figures are obtained. A greater number are known to be encountered in the warmer parts of the country. The number of rectal conditions other than hemorrhoids is very low. However, there seems no reason to doubt the validity of this finding.

Table 4 is taken from the files of the x-ray department. It lists the relative incidence of 1698 cases of disease recognizable by the x-ray. Peptic ulcer leads the list followed by carcinoma, gallbladder disease and diverticulosis in the order named. These conditions out-number the other disorders by a wide margin. The small number of benign tumors is similar to figures obtained from other clinics (1). Four occurred in the stomach, two in the duodenum and one in the gallbladder.

This table is useful for the conditions listed, but consideration must be given to the fact that there are certain organic diseases which cannot be determined roentgenologically or will not be referred for roentgen study. Inflammations such as pancreatitis and appendicitis usually give no hint of their presence by the x-ray. The roentgenologist is not likely to observe the rectal disorders such as hemorrhoids, ischio-rectal abscess, etc. Parasites are another condition which he will rarely diagnose.

In the 500 autopsy protocols which were studied, 303 or 60 per cent revealed histological changes in one or more of the digestive organs. One hundred and fifty-six of these 303 cases, or a little over one-half had more than one lesion, as shown in table 5. Five hundred and forty-three lesions were reported among the 303 cases. Of these, 324 were clinically important, 138 were of questionable clinical importance and 81 appeared of no import.

Disorders of accepted clinical significance are listed in table 6, which also gives their percentage to the 303 cases showing lesions and to the total of 500 cases making up the series.

The 138 lesions of questionable importance are presented in table 7. These were discussed with one of the hospital pathologists who believed that many of them could be and probably were of clinical importance, but that with our present knowledge we are unable to correlate the findings with clinical symptoms.

Autopsied cases are not strictly comparable to the clinical ones because they represent an older group of patients with disease sufficiently advanced to produce death. The ages ran from 13 to 92 years with an average age of 63,

TABLE 6

The number of gastrointestinal lesions of accepted clinical importance found in 500 consecutive autopsy records

	NO. OF LESIONS	% OF TOTAL CASES
Peptic ulcer.....	37	7.4
Gastric.....	10	
Duodenal.....	27	
Carcinoma.....	50	10.0
Esophagus.....	3	
Stomach.....	11	
Hepatoma.....	4	
Bile duct.....	5	
Pancreas.....	6	
Small intestine.....	1	
Colon.....	13	
Rectum.....	6	
Peritoneum.....	1	
Cholelithiasis and cholecystitis.....	97	19.4
cholelithiasis.....	95	
Without stones.....	2	
Diverticulosis.....	51	10.2
Esophagus.....	2	
Small intestine.....	18	
Colon.....	31	
Benign tumors.....	40	8.0
Esophagus.....	1	
Stomach.....	7	
Small intestine.....	6	
Appendix.....	1	
Colon.....	24	
Rectum.....	1	
Non-malignant diseases of liver.....	14	2.8
Cirrhosis of liver.....	13	
Acute yellow atrophy.....	1	
Non-malignant diseases of pancreas.....	8	1.6
Acute pancreatitis.....	4	
Chronic pancreatitis.....	3	
Pancreatic calculi.....	1	
Other conditions.....	27	5.4
Chronic esophagitis.....	5	
Hypertrophic gastritis.....	1	
Cicatrizing enteritis.....	1	
Non-specific ulcerative colitis.....	1	
Ulcerative colitis.....	2	
Intestinal tuberculosis.....	2	
Acute appendicitis.....	2	
Intestinal obstruction.....	6	
Intestinal thrombosis.....	7	
Total.....	324	64.8

as compared with an average age of 40 among the private patients. Seventy-five per cent of the autopsied cases were above 50 years of age; whereas, only 33 per cent of the private cases fell into this age group. However, they provide some means of checking our diagnostic abilities on the living patient.

RELATIVE FREQUENCY OF ORGANIC LESIONS

The most frequent organic lesions are peptic ulcer, carcinoma, appendicitis, gallbladder disease, diverticulosis, hemorrhoids and gastroenteritis (tables 3,

TABLE 7
Pathological lesions of questionable clinical importance

	NO. OF LESIONS
Esophagus.....	0
Stomach.....	6
Chronic gastritis.....	4
Aberrant pancreatic tissue.....	2
Liver.....	37
Cirrhosis, non-specific.....	9
Cirrhosis, portal.....	1
Cirrhosis, biliary.....	3
Fatty liver.....	20
Tuberculosis of liver.....	3
Amyloid.....	1
Biliary tract.....	20
Chronic cholecystitis.....	16
Chronic cholangitis.....	4
Pancreas.....	30
Fibrosis of varying degree.....	25
Dilatation of ducts.....	5
Small intestine.....	2
Melanosis.....	1
Aberrant pancreatic tissue.....	1
Appendix, fibrosed or scarred.....	33
Colon, melanosis of.....	10
Total.....	138

4, 6). The figures on peptic ulcer warrant consideration because its symptoms are the most definite and diagnosis by the x-ray is usually prompt and relatively accurate. The disorder was recognized in 4 per cent of the ward patients and 2.9 per cent of the outdoor cases, an average of 3.4 per cent for the entire hospital. This is an increase in the recognition of this disease of 1.6 per cent since 1929 when the incidence was found to be 1.8 per cent for the same hospital (2). An increase in the recognition of ulcer has been generally observed and has been attributed by some to an increase in the disease. How-

ever, the increase has occurred concomitantly with an improvement in roentgen diagnosis and has been accompanied by a decrease in the diagnosis of "hyperacidity." Therefore, improvement in roentgen technique is responsible for some, if not all, of the increased recognition and as such, should be a source of satisfaction to all. A previous study (3) at the Brigham Hospital has shown that the x-ray misses approximately 3.2 per cent of all ulcers. Using this figure as a corrective factor for the 40 cases recognized on the wards would raise the probable figure to 5.28 per cent. This figure agrees pretty well with the 7.4 per cent found at autopsy which is lower than the figure of 10 per cent which Hurst and Stewart (4) give for the probable incidence in England.

The disease was diagnosed in only 1.78 per cent of the private cases. Although some difference will exist between the samples because of chance, it is probable that failure to recognize the presence of the disease explains part of the difference as will be shown later. The incidence is greater in the outpatient department than in private practice, perhaps because the x-ray was used more frequently than in the private practice. The figure becomes still higher on the wards where the patients are even more systematically studied.

Table 3 shows that similar variations exist with disease of the gallbladder and the appendix. Gallbladder disease was recognized in 4.4 per cent of the ward cases; 1.6 per cent of the outpatient cases; and only 0.8 per cent of the private cases. It may be reasoned that the figure obtained from the ward patients is probably higher than occurs in the general community because many of these patients may have been sent for operation after the diagnosis had already been made. Likewise, Kantor's (5) incidence of 7.7 per cent in private practice may be higher than is encountered in general practice. However, the finding that 3 per cent of the autopsied cases had undergone a cholecystectomy is compatible with the ward figure of 4.4 per cent, since any error would presumably be on the low side. Therefore, the figure of 0.8 per cent in private practice appears out of proportion to the others and suggests again that quite a number of cases were not recognized.

The incidence for appendicitis was 3.2 per cent for the wards; 1.6 per cent for the outpatient department and 0.3 per cent for private practice. 7.4 per cent of the patients had lost their appendix by the time they came to autopsy.

The samples reveal similar discrepancies in regard to carcinoma, 24 cases being recognized on the wards, none in the outpatient department and 8 in private practice. The differences are difficult to analyze because there are so many variable factors of sex, age and conditions of study for the different samples. However, the pathological figure of 10 per cent, although slightly higher, agrees pretty well with the rate of 77.6 per 100,000 given in the annual report on the Vital Statistics of Massachusetts for the year ending December 31, 1938. Furthermore, our autopsy figure of 0.6 per cent for carcinoma of

the esophagus compares favorably with the figure of 0.4 per cent quoted by Mosher and MacMillan (6). Therefore, the pathological figure of 10 per cent appears to be accurate. Yet, carcinoma was recognized clinically in only 1.1 per cent of the 2839 cases observed in this study. In other words, of the 280 individuals who could be expected to ultimately die with carcinoma, only 32 persons were recognized as having the disease at the time of observation. Undoubtedly, many of these patients had not yet developed the disease, but it would be useful to know how many were missed.

A comparison of the x-ray and pathological figures is interesting. Although tables 4 and 6 cannot be compared directly, it is possible to make a satisfactory, indirect comparison by utilizing the ratio between carcinoma and peptic ulcer. The relative incidence of peptic ulcer and gastric carcinoma as recognized by the x-ray (table 4) agrees satisfactorily with the pathological findings (table 6). The x-ray recognized 605 cases of peptic ulcer to 221 gastric carcinomas, a relation of slightly over 3-1 (an index of 0.36). At postmortem there were 37 cases of peptic ulcer to 11 cases of gastric carcinoma, a relation of slightly less than 3-1 (an index of 0.297). Applying this method to all cases of gastrointestinal carcinoma, we obtain the results shown in table 8. This shows a surprisingly close correlation to exist between the x-ray and pathological findings in carcinoma of the esophagus and stomach, the two divisions of the tract which are most easily available for study by the x-ray. The correlation is not so satisfactory with the colon. This may be due in part to the fact that certain colonic lesions are not classified in the x-ray files as carcinoma because the roentgenologist could not be sure of their malignant nature and reported them merely as obstructing lesions. It is well known that many cases of carcinoma of the liver, pancreas and rectum cannot be recognized by the x-ray. This is borne out by table 8.

Because the x-ray is our best means of recognizing gastrointestinal carcinoma, the results in table 8 would indicate that a failure to recognize the disease is partly responsible for the difference between the pathological and clinical findings. We have already shown a difference of 4 per cent between the clinical recognition of peptic ulcer and the autopsy figures and that a previous study revealed a failure to recognize 3.2 per cent of these cases by x-ray. If this situation is true for a disease limited to the stomach and duodenum, it would seem that a similar or greater error must exist for malignancy which may involve any portion of the tract.

The figures concerning diverticulosis and cancer have much in common. Ten cases were recognized on the wards, none in the outdoor department and 5 in private practice. This is an incidence of 0.5 per cent for the series as compared with 10 per cent for the autopsied cases. As would be expected, gastroenteritis was encountered more often in private than in hospital work.

Three cases of benign tumors were recognized clinically, an incidence of 0.1 per cent as compared with 8 per cent at autopsy which is about the usual reported finding (1).

FUNCTIONAL DISORDERS

Of those patients complaining of gastrointestinal trouble, 10.5 per cent of the ward patients, 53.8 per cent of the outpatients; and 59.6 per cent of the private cases were thought to be functional (table 2).

The figures are so diverse as to mean little without further analysis. The small number of functional cases found on the wards can be easily understood. Patients suspected of functional disorders are usually not referred to the wards which receive a large proportion of the more serious organic diseases. There-

TABLE 8

Shows the relative effectiveness of the x-ray in recognizing gastrointestinal malignancy depending upon its location as compared with a pathological study. The method of obtaining the indices is described in the text. The table reveals the x-ray to be most useful in diagnosing malignancy of the esophagus and the stomach, somewhat less useful in colonic malignancy and of relatively little value for malignancy of the remaining organs

	PATHOLOGY INDICES	X-RAY INDICES
Esophagus.....	8	7
Stomach.....	29	36
Liver.....	10	0
Bile duct.....	13	0.8
Pancreas.....	16	1.3
Small intestine.....	27	0.3
Colon.....	35	23
Rectum.....	16	6.1
Peritoneum.....	2	0

fore, the low figure of 10.5 per cent may be dismissed from further discussion. The figure of 53.8 per cent obtained from the outpatients has been criticised by some of my colleagues on the ground that it was too low and that these patients did not portray the conditions existing in the community. The figure of 59.6 per cent obtained from the private practice is more in line with the usual impression that the functional cases outnumber the organic by a large margin. However, a study of the private patients included as functional indicates that this figure is probably too high. These cases have been listed as functional because the records gave no evidence that the physician considered them to be organic. However, the records rarely stated a definite impression and it may be possible that the physician considered some of them organic which I assumed he had accepted as functional.

One gained the impression that in many instances a functional diagnosis was assumed because of the presence of nervousness or some cause for worry, without adequately ruling out organic disease and without any clear demonstration of an association between the two. Only 14 patients, or 11 per cent had complete x-ray studies. Less than 3 per cent of the 122 diagnosed as functional had a complete gastrointestinal examination, including studies of the stools, gastric analyses and x-rays. Fifty-seven patients had no x-ray studies. Of the remaining 51 cases, 45 x-rays of the upper gastrointestinal tract were made, 8 barium enemas and 8 cholecystograms. The stools and gastric contents were examined in only 13. Only one patient had a proctoscopic examination. Therefore, the possibilities of missing an unsuspected organic lesion are very real.

Evaluating the cases as well as possible from the available information, I came to the following conclusions: There were 50 cases which appeared to be clearly functional. There were 46 others about which it was impossible to draw any conclusions. There was nothing in the record to indicate a functional rather than an organic cause for the symptoms. Many of these had no special studies and some were seen only once. There were 26 patients about whom there was highly suggestive evidence that organic disease was responsible for the symptoms, but no serious attempt was made to prove this. There were 9 in this group who may have been suffering from an unrecognized ulcer. One was found to have ulcer when he returned nine years later. His symptoms had been the same throughout this time. A diagnosis of duodenitis was made by x-ray on 3. The diagnosis of ulcer was not entertained in two cases, apparently because of one negative gastrointestinal series and no further studies were made. Only one of the other 6 patients had any special study and that was a barium enema.

Of the remaining 17 patients in the original 26, there was reason to believe that 6 may have had a diseased appendix. A surgical diagnosis of subacute appendicitis was made on one, but nothing was done about it. Another case continued to have symptoms for 2 years and relief followed the removal of the appendix and one ovary.

There were 11 other patients in whom there was evidence to suggest the following conditions: hypoglycemia, Addison's disease, common duct stone, vitamin deficiency, diverticulitis and the last case suggested that the pain came from the back.

Therefore, it appears that the figure of 59.6 per cent for non organic disease is too high and that the incidence of functional disorders of the gastrointestinal tract was around 50 per cent in both the outdoor department and private practice.

COMMENT

Judging from conversations with numerous physicians on the subject of functional disorders, some will read these figures with surprise and skepticism simply because the general concensus of opinion seems to be that the functional outnumber the organic cases by at least 3-1. What evidence is there for the correctness of the data in this series? They are in harmony with a similar investigation made by Gregg and Snowden (7) in which 1150 or 53 per cent of 2189 patients with gastrointestinal symptoms had organic disease. My own practice shows 54% with organic disease. Chamberlain (8) reported that of the admissions to the gastrointestinal service of the Lawson General Hospital of the Army, 65 per cent was for organic disease. Rush (9) reporting on gastrointestinal disturbances in the combat area stated that of 200 patients admitted to a large hospital in the South Pacific because of "dyspepsia" 53 per cent were subsequently judged to be functional, giving an incidence of 46 per cent for organic disease. Although the circumstances underlying these statistics are variable, one cannot escape the close similarity of all these figures when careful studies are made. Therefore, statistical studies indicate that the incidence of organic and functional disorders, as we now think of them is about the same.

Nevertheless, one cannot dismiss lightly the opinions of the many and one may well ask why these figures are at variance with the usual impression. Of course, it is always possible that a general impression is incorrect and that a survey of one's records will reveal the error.

However, the most important factor appears to be that the word functional is used loosely and without benefit of any exact meaning. To some, it means a patient in whom no organic disease has been found. Using the word this way means that the incidence of functional disorders depends upon the ability of the physician to make a diagnosis as well as the thoroughness with which the patient is studied. Every case in which an organic lesion is missed automatically increases the functional disorders at the expense of the organic diseases.

Some physicians apply the term to conditions such as gastrointestinal allergies because our diagnostic methods cannot demonstrate tissue changes which, however, are known to be present. This use of the term merely distinguishes between those disorders which produce tissue changes usually demonstrable by our present diagnostic methods and those which usually do not. To some, functional is synonymous with psychogenic. This confusion over the meaning of functional is not new. A perusal of the medical dictionaries reveals a striking lack of conciseness regarding the many and varied definitions for all terms used to describe the so-called functional disorders. The present

interest in psychosomatic medicine has resulted in a wave of popularity for such terms, with physicians using them to describe any disease that does not readily fall into the group of easily demonstrable organic lesions. The use of words with indefinite meanings leads to confusion of ideas and interferes with medical progress. Recently, one of my younger colleagues questioned whether the relative incidence of the diagnosis of functional and of organic disease was important. Its importance consists in determining how accurately we diagnose our patient and how intelligently our patients are being treated.

This investigation has shown a gratifying correlation between the clinical and pathological figures only for some lesions and under certain conditions. A study of the data indicates that the best correlation exists for those lesions which are easily recognized by the x-ray, such as carcinoma of the esophagus and stomach, peptic ulcer and gallbladder disease. Disorders such as pancreatic lesions which are not readily susceptible to diagnosis by the x-ray and must be looked for by the more time-consuming methods of repeated stool examinations and intestinal intubations are more often missed. The diagnostic accuracy decreases in the outpatient department and still more in private practice. As previously pointed out, there is evidence that at least part of the difference results from a failure to completely work up the patient. Accurate gastrointestinal diagnoses depend upon the adequate use of all available laboratory studies. It is not justifiable to eliminate organic disease by symptoms alone. Patients with gastrointestinal complaints are entitled to and should receive complete studies. This requires that all necessary laboratory studies should be available for all patients, at a cost that will encourage, rather than dissuade them to have such examinations.

This study also reveals that as the number of organic diagnoses decreased, the number of functional diagnoses increased.

One has to guard against falling into a vicious spiral. A failure to diagnose organic disease gives a false impression of the number of functional disorders. This impression seems to justify the relatively low incidence of organic disease. Add the present tendency to lean on the psyche for otherwise unexplained symptoms and we are in danger of misleading ourselves and mistreating our patients.

In this connection, the study of the autopsied patients presents data for thought. As previously pointed out, 303 cases of 500 showed 460 pathological conditions of the gastrointestinal tract. Two hundred and eighty-eight or 62 per cent of those 460 were of accepted clinical importance. But there were also 147 lesions or 33 per cent of possible clinical importance. These were not diagnosable by our present methods of study. Unfortunately, we do not know how many of these conditions may, or were capable of giving symptoms.

However, it is reasonable to suppose that these conditions were responsible for a certain number of symptoms. The number of these lesions represents half of the pathological conditions which are now recognized to be of clinical importance.

Such evidence suggests that with greater knowledge the number of functional diagnoses should continue to decrease. Meanwhile, a clarification of the meaning of the terms in current use such as functional, nervous, etc. would be a distinct contribution to medicine. In the attempt to teach medical students to formulate a definite opinion, we have demanded a definite diagnosis. In reality, the use of some descriptive term such as "gastrointestinal symptoms, cause unknown" might result in clearer thinking.

SUMMARY

A statistical study has been made to determine the incidence of gastrointestinal disorders. A total of 2,839 patients were studied from 3 samples: 1,000 consecutive ward patients from the Peter Bent Brigham Hospital; 1,000 consecutive outpatients and 839 patients from a general practice. In addition, 500 consecutive autopsy reports were studied.

The investigation reveals that approximately 19 per cent of patients apply for relief of gastrointestinal symptoms.

The data show that approximately 50 per cent of these patients have organic disease in the accepted sense of the term. The recognition of organic disease was greatest in the ward patients, next in the outpatients and lowest in the private patients. These differences were found to depend in part upon a greater number of patients entering the hospital with organic disease; and, in part, upon the thoroughness with which patients are studied.

The investigation emphasizes the need for a greater use of the x-ray and other laboratory facilities in the diagnosis of patients with gastrointestinal complaints.

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REGIONAL ENTERITIS IN PUERTO RICO

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INTRODUCTION

Acute segmental enteritis is a frequent disease among native-born Puerto Ricans. In the past two years resections for acute stages of the disease have been performed in fifteen cases at the Bayamón District Hospital.

Generally speaking, diseases of lymphatic origin predominate in the tropics, where many sprue-like conditions and lymphogranuloma are common.

Acute regional enteritis in Puerto Rico is clinically an emergency condition which usually presents the picture of an acute medical abdomen provided one elicits three clinical signs: 1) high leucocytosis 18 to 30,000 with a normal or relatively low neutrophile percentage, and a high percentage of eosiniphilia; 2) tarry stools; 3) flaccidity of the abdomen out of proportion to the acute, intense abdominal pain in a great majority of cases.

It should be admitted that it is difficult for an internist to be certain of the diagnosis on the basis of these signs but usually if in doubt he suggests surgical intervention. This factor has been solely responsible for finding the very acute phases of regional enteritis in younger people.

The symptoms described by other observers are more representative of the chronic type of disease. The symptoms I have seen follow a clinical evolution of a sprue-like syndrome of the disease.

A DESCRIPTION OF THE SYMPTOMS

The abdominal pain is severe and excruciating with intermittent cramps which are not particularly associated with nausea. The pain is not associated with shock. Morphine and atropine gives only temporary relief from the pain. There is no fever usually.

Palpation of the abdomen reveals an indefinite tenderness without rigidity; in some cases rebound tenderness may be elicited, while in others there is a characteristic doughy feeling.

The laboratory findings are negative except for a high leucocyte count. The blood chemistry is normal in most cases. Occult blood when persistently present in the daily stools indicates an unfavorable prognosis. Intestinal parasites are invariably present. The x-ray examination of the chest is negative for tuberculosis.

The age of the patients varies from 14 to 35 years. The history is relatively negative in regard to gastrointestinal disorders, except in the cases in which

definitely chronic regional enteritis is present. At the onset of the acute condition most of the patients have no diarrhea or constipation; in others the onset simulates acute colitis. In the chronic condition there is a history of dyspepsia and digestive complaints which resemble those of sprue.

It was sometimes difficult to determine whether the patients should be carefully watched or should be subjected to surgical intervention. Evidence of allergy could not be elicited, a history of asthma and sinusitis being obtained in only 5 of 26 cases.

A tentative diagnosis of acute mesenteric lymphadenitis was made, the condition being preponderant in children rather than in adolescents and young adults. Exploratory laparotomy, when performed, was undertaken under the diagnosis of suspected acute appendicitis.

SURGICAL AND POST-MORTEM PATHOLOGY

Five types of pathological changes have been observed. (1) Multiple mesenteric adenopathy with segmental congestion of the small intestine. Appendectomies were performed on these cases and biopsies of the mesenteric glands were made. (2) Acute ulcerative ileitis or jejunitis of undetermined cause. (3) A segmental stenosing regional enteritis with lymphedema and areas of gangrene suggesting strangulation. (4) Chronic strictures with giant cell tubercles and pathology as described by Hadfield. (5) Schistosomal regional ileitis, representing a phase of mesentery adenopathy in which the ova affected the mucosa and subserosal lymphatics causing a regional ileitis.

The pathologist has not been reconciled to view such cases as regional ileitis. In order to diagnose a specimen as regional ileitis, he must find the authentic Hadfield criteria for giant cell tubercles. However, Dr. H. L. Bockus, who inspected our specimens during a recent visit, states that Hadfield's pathological criteria can be found in 30 per cent of cases.

Fifteen cases were described as follows: (1) Hyperplastic lymphadenopathy with diffuse submucosal edema and intense cellulitis, i.e., round and plasma cell infiltration and dilation of the lymphatics (8 cases). (2) "Skip lesions" in which nodular areas of thickening alternated with thinning and haustration of segments of the intestine (3 cases). (3) Grossly tubular fibrotic stenosing form of enteritis, or the advanced chronic stage (4 cases). Tuberculosis was ruled out by Ziehl-Nielsen staining of the tissues.

The following case report illustrates a transitional phase between acute and chronic lymphadenitis with the development of acute regional enteritis.

Case No. 27220: A child seven years old was referred from a nearby town with a history of pain in the right lower abdomen and bloody stools of five days duration. His pains were crampy and associated with bloody mucus in the stools. On admis-

sion the child developed acute fever, 38°C , pulse 20, respiration 44. He was seriously ill

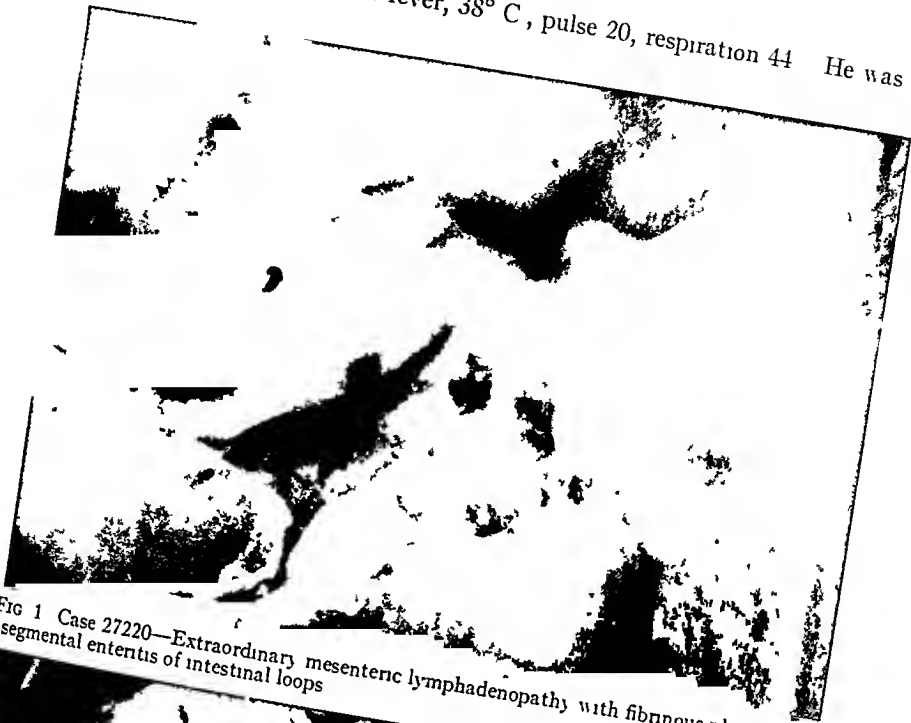


FIG 1 Case 27220—Extraordinary mesenteric lymphadenopathy with fibinous plastic exudate, and segmental enteritis of intestinal loops

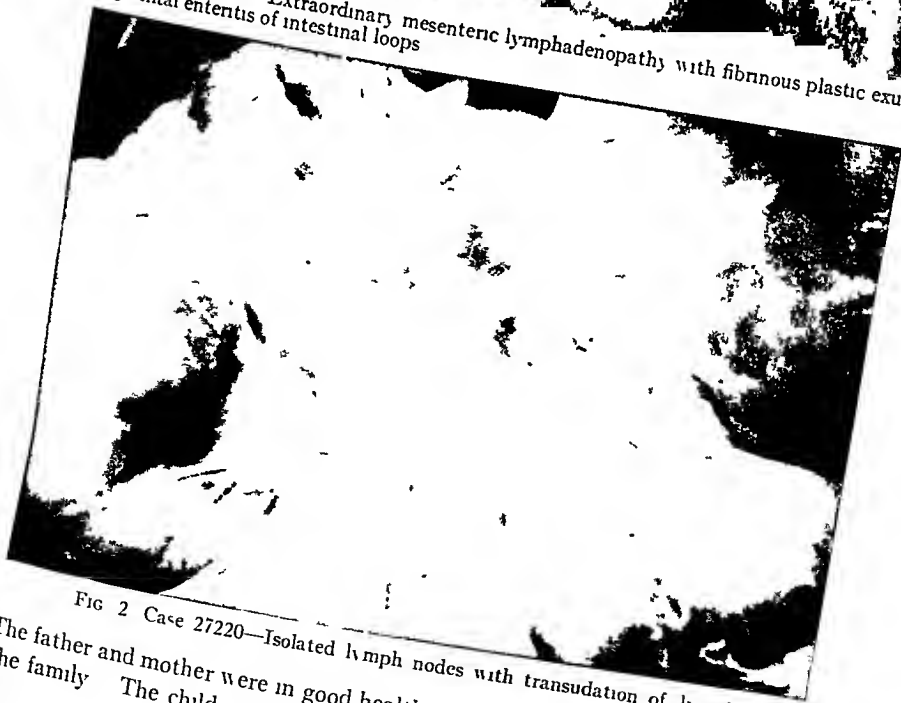


FIG 2 Case 27220—Isolated lymph nodes with transudation of lymph

The father and mother were in good health. There was no history of tuberculosis in the family. The child was a normal delivery but was in poor gastric health for

some time previously. Physical examination revealed a normal, well developed, dark-skinned child, anxious and acutely ill. The abdomen was painful, not particu-

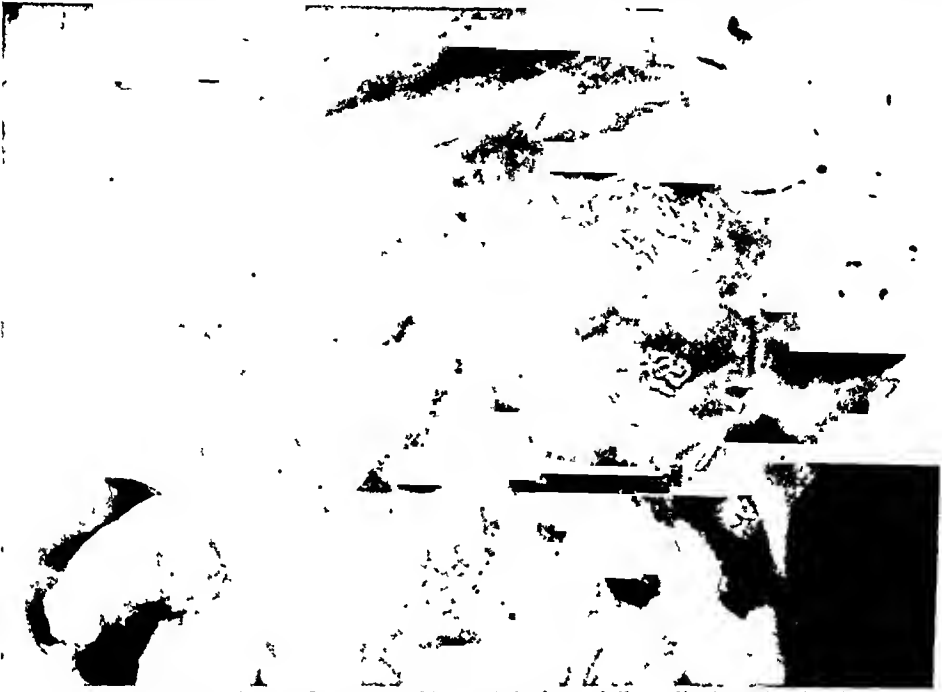


FIG. 3. Case 27220—Hypertrophic nodulation of ileocolic lymph glands



FIG. 4. Case 27220—Isolated gangrene of a mesenteric nodule. This particular case had staphylococcus albus septicemia

larly rigid, but rather doughy, without sufficient point-tenderness to justify surgery. R.B.C. 3,640,000; W.B.C. 18,850; Hb. 53 per cent; Seg. 80 per cent; Stab. 5 per cent;

Lymph. 14 per cent; Eos. 1 per cent. Urinalysis showed albumin; sugar negative; and the microscopic examination showed the presence of renal epithelial casts and

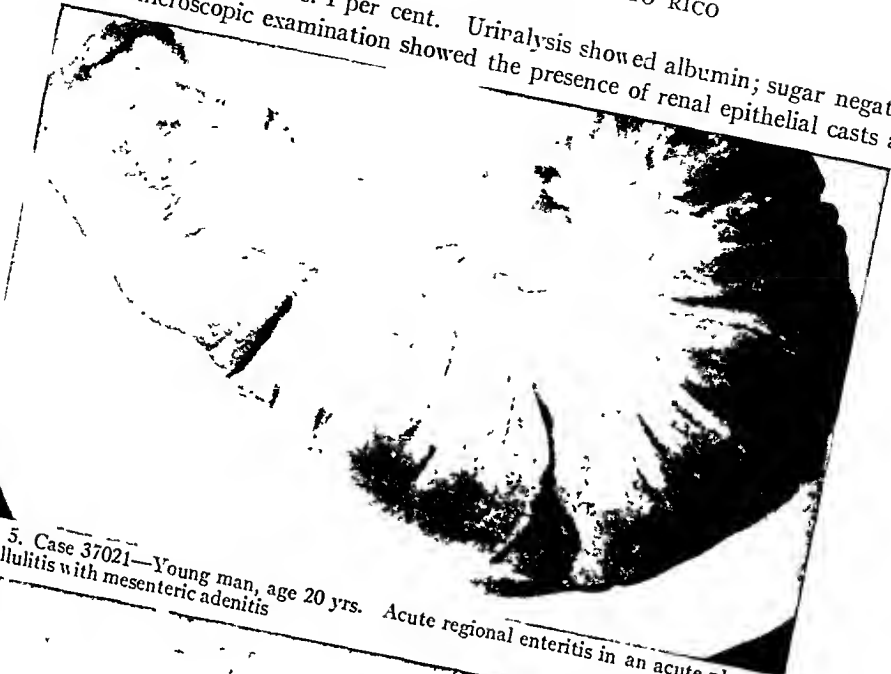


FIG. 5. Case 37021—Young man, age 20 yrs. Acute regional enteritis in an acute phase of intense cellulitis with mesenteric adenitis



FIG. 6. Case 37021—Young man, age 20 yrs. Mucosal surface showing much submucosal edema and thickening. mucous threads. Kahn and Kline tests were negative. The blood culture for typhoid was negative. Staphylococcus albus of a non-hemolytic variety was present in the blood culture.

An exploratory laparotomy was performed. There was a diffuse exudative peritonitis over one segment of ileum well localized over the right lower quadrant. The appendix was normal. An extensive mesenteric lymphadenitis involving all segments of the ileum and jejunum of the left upper quadrant was found. Regional ileitis was definitely present with a diffuse mesenteric lymphadenopathy. A biopsy

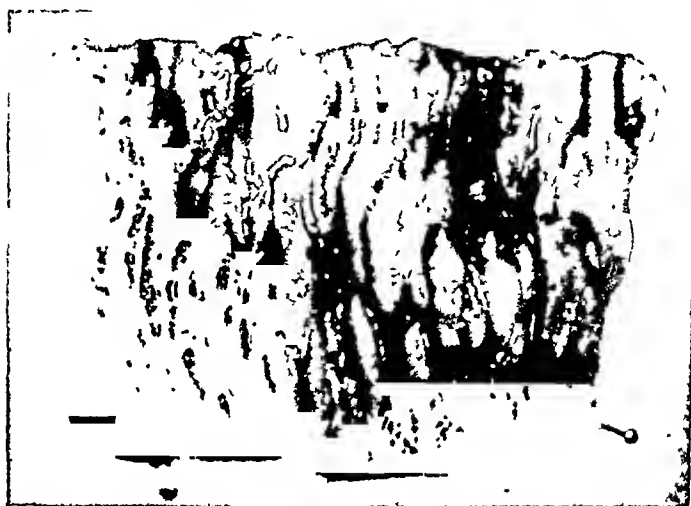


FIG. 7. Case 27667—Mucosal appearance of a case of acute segmental enteritis found in a young boy of 17.



FIG. 8 Case 27367—Lumen of intestine displaying extraordinary mucosal thickening

of a lymph node was taken. The abdomen was closed immediately without removing the appendix. The child died on 8/21/43. A partial autopsy of the case was made and the whole of the abdominal viscera was removed. Different pictures are shown in figures 1 to 4. In figure 1 there is a clear demonstration of the plastic fibrin over the ileum which resembled a perforation. This was not confirmed microscopically.

The extensive lymphadenopathy of the mesentery with profusion of mesenteric nodules the size of peas to the size of lima beans is shown in figures 2 and 3. Figure 4 depicts the different phases of extensive lymphadenitis with the brownish mottling of gangrene among solitary nodules. Some loops of ileum were filled with brown chocolate material suggestive of digested blood.

The pathological records follow: *Gross*: The specimen consists of a small lymph node measuring 1 cm. in main diameter. *Microscopic*: The capsule is of uneven thickness and shows areas of edema with infiltration with small lymphocytes. The pulp contains lymphoid follicles. The sinuses are very greatly dilated and contain numerous littoral cells. There is a generalized sprinkling with lymphocytes and polys. *Diagnosis*: Acute and chronic lymphadenitis of mesenteric lymph node.

Autopsy findings of the intestinal viscera: *Gross*: The specimen consists of the entire small intestine attached to the mesentery, received 4 days after post-mortem removal.



FIG. 9. Case 27367—Edema of intestine

The upper portion of the jejunum for a distance of 24 cm. appears slightly darker than the remaining intestine through the serosa. The mesenteric lymph nodes are larger than normal and slightly hemorrhagic. On opening the intestine the lumen is seen to be filled with a dark brownish liquid. The upper slightly-discolored jejunal portion shows a somewhat darker than normal mucosa. The walls are somewhat broader than normal. The remaining intestine shows autolysis of the mucosa. *Microscopic*: Autolysis is marked. Large areas of the mucosa are necrotic. Numerous polymorphonuclears and plasma cells are present in these areas and in the submucosa just beneath it. Generally, the submucosa is greatly broadened by edema and moderately infiltrated by polys and plasma cells. The muscle coats and subserosal tissues show slight edema. Numerous pigment-laden phagocytes are scattered here and there. *Lymph node*: The sinuses are markedly dilated and there is desquamation of littoral cells. There is no increase in the number of polymorphonuclears. The germinal centers are not active. Numerous pigment-laden phagocytes

are scattered throughout. *Diagnosis:* Acute regional enteritis; chronic lymphadenitis.

Figures 5 to 10 are specimens of regional ileitis ranging from edema and thickening of the folds of mucosa to edema of the entire wall of segments of the small intestine.

TREATMENT OF REGIONAL ILEITIS

The treatment of regional ileitis is so far as we know surgical. Garlock and Crohn have devised an ileal exclusion of the diseased segment, and ileo-transverse colostomy.

It is my personal impression that the disease calls for medical treatment,



FIG. 10. Case 28902—C. R. This patient had pinworms. Note the thickened indurated folds. This patient had skips lesions of thickened areas alternating haustrations.

in the acute stages. As has been said, it is an acute medical abdomen. When one faces a definite cellulitis of an enteric segment, conservative management is definitely preferable to intestinal resection. On the other hand one has to admit that ileal resections are very satisfactory operations, and of recent, resections of the ileum, and cecum, with ileocolic anastomosis have been in my experience very successful surgical procedures. Patients have recovered without fistulization from ileocolic resections in 14 out of the total 15 so far proven cases of regional ileitis. No fistulization has so far developed in these cases. The follow-up during two years has not classified them as entirely well from ill-defined dyspepsias, and much is yet to be done on a dietary basis to restore their health.

The pathology of the intestine should be considered in relation to cases of mechanical extrinsic strangulation of intestine, a series of cases of which has also been studied. In the operating room many cases of strangulation edema of the intestine come as acute emergencies, characterized by similar signs of segmental pathology. These cases have the distinct gross and microscopical pathology of an acute inflammatory reaction with much serosal hemorrhage and mucosal edema. Edema of the intestine is usually near the ligament of Trietz, in most cases it involves the jejunum, and the lymphoid hyperplasia of the mesentery is well pronounced over this area. But these cases are not difficult to distinguish pathologically from regional ileitis. These patients recover uneventfully from their resections.



FIG. 11 Case 28902—C R Segmental enteritis in the form of a regional congested segment with obstructive edema

DISCUSSION

We are inclined to believe that in our cases of regional ileitis we have been observing a progressive functional disorder of the lymphatics.

The cases of acute and chronic lymphatic involvement may represent early stages of the disease. In such cases clinically an appendectomy is performed, but the disease continues. Hadfield's pathological criteria develop in the well-defined fibrotic stage of the disease. There is no clear cut evidence of a specific bacterial genesis of the disease in our cases and throat conditions are not correlated with mesenteric lymphadenitis. We believe that nutritional deficiencies increase the incidence of the disease in Puerto Rico. A deterioration of the physical condition and the youth of our patients impresses us

The invariable presence of intestinal parasites does not particularly impress us as having a specific etiological bearing. Food or bacterial allergy does not impress us as being a specific cause.

Various manifestations or types of the disease under discussion have been described clinically. They are: an acute type simulating appendicitis, a type causing ulcerative enteritis, another causing small bowel obstruction, and a final type characterized by persistent intractable fistulas occurring either spontaneously or following an operation.

Crohn and Yunich define the disease as an ileojejunitis characterized by ulcerative granulomatous lesions which cause symptoms which may simulate those of non-tropical sprue and the intestinal manifestations of certain nutritional deficiency diseases.

Rieben in Germany quotes Sproull's 132 cases in which the terminal ileum was involved in 37 per cent, ileum and ileocecal valve in 13 per cent, ileum and cecum in 25 per cent, the cecum in 8 per cent, and other parts of the large intestine in 1.5 per cent, and the jejunum in 4 per cent of cases.

The recent literature on the subject contains a number of interesting reports of cases. Allen and Bell describes the disease in Australia and Marshall reviews 48 cases seen during six years at the Lahey Clinic. Crohn and Penner describe other varieties of the disease in which fistulous tracts develop as complications.

Ginzburg and Garlock, Eliason and Johnson, and Fallis discuss the surgical and pathological considerations, all of which represent the common experience in our hospital as well. Brown and Donald review 178 cases of regional enteritis from the Mayo Clinic. Among the 178 cases, 82 had been operated on one or more times. In 42 cases fistulas occurred. There were 16 postoperative deaths and 17 deaths due to the same condition later in life.

My personal experience viewed in our hospital is that the postoperative course in regional enteritis is milder in Puerto Ricans, because of the relative absence of postoperative adynamic ileus in the surgical wards. While Gius and Paterson present a critical review of postoperative ileus (*Surg., Gynec. & Obstet.*, Oct., 1944), I am pleased to find that this is the least of our postoperative worries in abdominal surgery. When it does occur, we are usually faced with peritonitis and infection.

Regional enteritis has been introduced to the medical profession as an enteric disturbance without fully considering that the fundamental etiology probably lies in the lymphatic obstruction of the mesentery. The extraordinary review of Wilensky on lymphadenopathy has influenced American thought to believe that mesenteric lymphadenopathy is a clinical entity. In the support of my contentions I have not added new ideas on the subject because Bockus in his

latest textbook brings forth similar conclusions although in a speculative manner.

SUMMARY

Evidence is presented which leads the author to believe that regional enteritis is a functional disorder of the lymphatic system of the intestinal tract, which gives rise to phases of hyperplasia, "skip lesions" of intestinal fibrosis alternating with haustration, and fibrotic stenoses.

We have been concerned in this paper chiefly with acute cases of regional enteritis which we have seen as emergencies. They are conceived as acute medical abdomens because of the disproportion between the clinical signs and the acuteness of abdominal pain in young adults. We have been concerned more with what we consider to be the acute stage than with the commoner varieties of the chronic stage.

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EPIDEMIOLOGICAL STUDY OF AN OUTBREAK OF INFECTIOUS HEPATITIS*

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INTRODUCTION

Infectious hepatitis stood out as one of the most important medical problems of the recent war and, in spite of extensive studies, its epidemiology is not yet fully understood. The problem can only be solved by the collection and analysis of data on many epidemics, and it is with this purpose in mind that these observations are recorded on an outbreak that occurred in a Pennsylvania industrial city during the winter of 1944-45.

The city, situated on the banks of a tidal river, serves as a seaport and specializes in heavy industries such as shipbuilding, automobile manufacturing and the like. The normal population is about 60,000 persons but during the war this number was considerably increased by an influx of workers. A total of 52 cases of hepatitis was recorded between October and April, the majority occurring in January and February. There were probably considerably more cases than this for the investigation was not begun until spring, by which time the local physicians were unable to recall the names of many of their patients.

DISCOVERY OF THE OUTBREAK

The manner in which the outbreak was discovered is significant. A patient himself a physician, was referred to a Philadelphia consultant for study of jaundice. Examination and studies led to the diagnosis of infectious hepatitis. Because of local interest aroused by the hepatitis investigations of Neeffe and Stokes (1) an effort was made to discover the source of infection in this patient's case. The city physicians were questioned and the majority stated that they had been seeing more cases of jaundice than ever before. One physician had seen thirteen cases in three weeks. No one, however, realized that a distinct outbreak was occurring throughout the city. This demonstrates the important fact that an epidemic may exist within a city without the knowledge of the public health authorities. As infectious hepatitis in epidemic form can be a public health problem of considerable significance (1) and since, as in this instance, an epidemic can be unrecognized, it would seem desirable that legislation be passed to make infectious hepatitis a reportable disease. If it had not been for the current investigation being conducted in this hospital the outbreak would never have been discovered.

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OBSERVATIONS

Collection of data. The only cases investigated were those with visible jaundice, and information concerning them was obtained largely from the local physicians. A few of the patients were able to give the names of other cases. The residence of each case was visited and data were collected concerning the occupation or school attended, contacts (2), water, milk, food, insects and vermin (3, 4). Inquiry was also made concerning any previous medication or procedures involving the use of hypodermic needles (5). Information concerning the water and sewage systems was obtained directly from the municipal bureaus involved.

Age and sex incidence. The cases occurred chiefly among school children, the highest age incidence being between 5 and 9 years. In only 2 out of 30 families in which one or more children had hepatitis did a parent contract the illness. 21 males and 31 females were affected.

Age	Males	Females
1-5 years.....	3	8
6-10 years.....	7	14
11-15 years.....	5	2
16-20 years.....	2	4
21-30 years.....	3	2
over 30 years.....	1	1

Course of the epidemic. The first recorded case in the city occurred in October, 1944. No cases were then discovered until the end of November, after which cases appeared regularly. A sharp rise in the number of cases occurred toward the end of December, the incidence reaching its peak early in February and declining progressively from that time on.

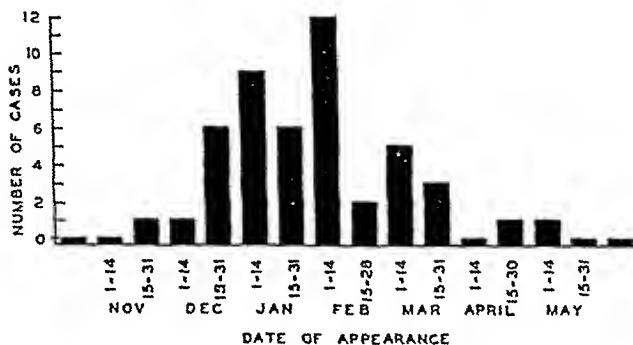


FIG. 1. Graph showing the incidence of cases appearing at two-week intervals. Only cases with visible jaundice are recorded.

Family incidence. The number of cases in single households varied greatly. In one family 6 of 7 children contracted the illness, while in a second, 4 of 5

children were ill. Usually, however, only one or two children in a family were sick. In some instances when one child had jaundice, one or two others had such symptoms as malaise, anorexia, or diarrhea, which may well have been hepatitis without jaundice. These cases were not recorded because of the uncertainty of diagnosis. Surprisingly often, however, one child was jaundiced while all other members of the family remained perfectly well.

Clinical history. The majority of the cases had similar histories. The illness began with anorexia, fever, malaise and marked drowsiness. After about a week nausea, vomiting, dark urine and finally jaundice appeared. With the onset of the jaundice considerable improvement in the general symptomatology usually occurred, and in most instances the jaundice lasted only a few days or a week. It seems improbable that this was Weil's disease, since a white blood count done in 5 cases was not elevated; also, agglutination tests and guinea pig inoculations performed with specimens from the most severe case were negative for that disease.

Epidemiology. The greatest concentration of cases, 20 in all, occurred in a new government housing project. This was made up of modern brick and concrete apartment houses accommodating about 150 families. The inspector from the city sewage department stated that the plumbing was of good quality and well installed. Another group of 7 cases occurred in and around a second housing project located a mile distant from the first. The remaining cases were scattered through the town but the majority fell near a line running across the center of the city.

The investigation made into the various possible factors involved in the epidemic gave the following results:

Milk. Milk was supplied by 5 different companies.

Food. No single store or source of food was employed by all the cases. Most of the families did visit branches of the large chain store systems. The families rarely ate out and had not visited any common restaurant.

Schools. Eight different schools were represented. No common source of milk or cafeteria supplies was found and several schools provided no food at all.

Medications. There was no type of medication common to the group. Only 2 children had undergone procedures involving hypodermic needles during the previous year.

Insects and vermin. The epidemic occurred during an unusually severe winter so that flies, mosquitoes, or other insects cannot be considered an important factor. None of the families complained of rats, mice or other vermin.

Cross infection. Cross infection by contact could explain some of the cases. In each of the housing projects the children played together and attended schools nearby. There was no contact, however, between the children of the two housing projects.

Water supply. The city obtains its drinking water from the river at a point near the center of the shore line. Contamination of the river by raw sewage at points near the source of water supply frequently occurs because the sewage system is so constructed that during severe storms the sewers may drain directly into the river in several places. Ordinarily the sewage is collected and treated before being discharged.

Treatment of the water consists of aeration, chlorination, coagulation with aluminum sulfate, treatment with clay and carbon, sedimentation, filtration and a final chlorination to leave a residual of 0.7 to 0.9 parts per million of water. The preliminary chlorination varies from 19 to 110 pounds per million gallons depending on the condition of the water.

After treatment the water is pumped into the city system, with excess water flowing to the reservoir at the opposite side of the city. Thus the flow in the pipes may be in either direction, for during the night water tends to flow chiefly to the reservoir while during the periods of peak demand the water flows away from the reservoir. This leads to considerable dilution in most of the system, but in the vicinity of the pumping station the flow is always directly from the river.

DISCUSSION

Analysis of the data collected in respect to the epidemic demonstrated that no common source of milk or medication was present while the role of insects and vermin seemed to be negligible. It did not seem likely that food could be incriminated for though most families at one time or another visited branches of the chain stores, these stores serve a large region and the outbreak was limited to the city.

Droplets from the nasopharynx of infected persons cannot be eliminated as the method of transmission to certain of the cases because of the close contact of some of the children as discussed above. No contact occurred, however, between the children of the two projects. In 11 of the scattered cases no contacts of any sort were known while in the case of a two year old only child the parents claimed she had had no exposure at all to other children. Also, early in the outbreak, cases occurred simultaneously in rather widely separated regions of the city, implying a common source of infection rather than a person-to-person spread. Furthermore, Neeffe and his associates (1) have pointed out that the causative agent apparently is not easily acquired by simple exposure. For this reason, it seems probable that contact transmission did not play a major role in the epidemic.

The most striking feature of the epidemic was the concentration of cases in a zone running across the center of the city while very few cases occurred throughout the other districts. Investigation demonstrated that this zone

followed closely the course of the municipal water main. The accompanying map demonstrates the distribution of cases and their relation to the water system. It must be fully understood that this map is very incomplete, being drawn in skeleton form for the sake of clarity. Side branches of the water mains run to all parts of the city, but these have been omitted in areas where no cases occurred. It is of particular interest that the chief water main runs right through the housing project most severely affected.

Neeffe and associates (1) have shown that the causative agent of infectious

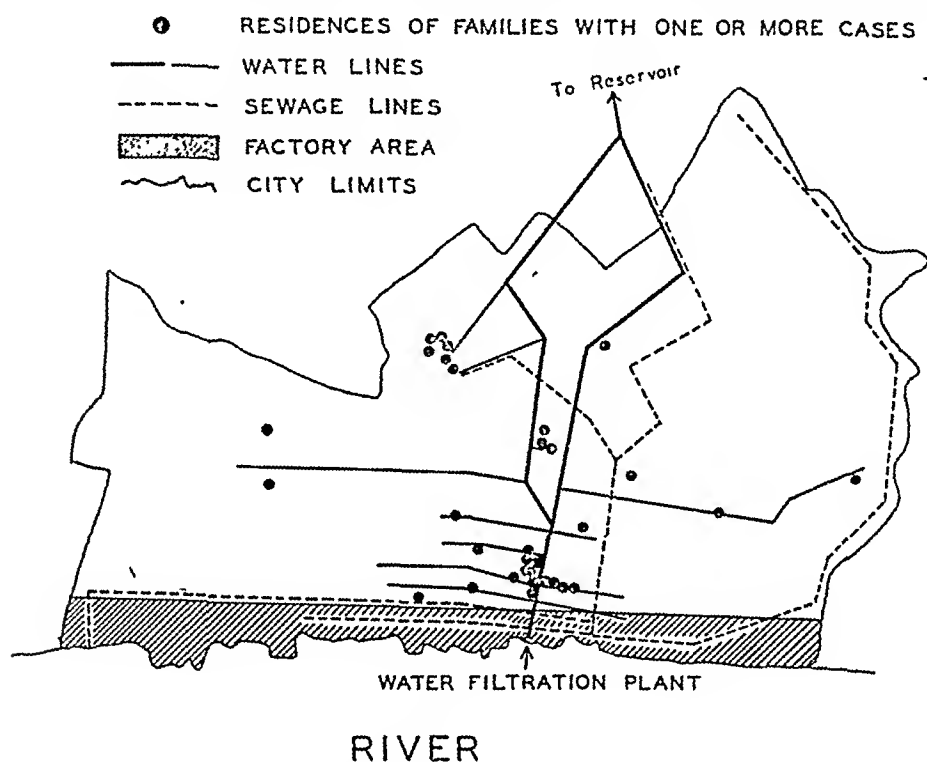


FIG. 2. Map of the city to show the distribution of cases and their close relationship to the pumping station and principal water mains. It is in these areas that the concentration of infective agent would be highest.

hepatitis can be transmitted by drinking water that has been contaminated by the excreta of persons suffering from the illness. The water supply of this city is not infrequently contaminated by raw sewage and, though the water is treated, Neeffe et al. (6) have also shown that a causative agent of infectious hepatitis in heavily contaminated water was not inactivated by treating with sufficient chlorine to provide a residual concentration of 1 p.p.m. after thirty minutes contact. Thus it seems possible that the causative agent occasionally might survive municipal methods of water treatment.

Finally, it is apparent (6) that the incidence of the disease will depend in part on the concentration of the agent, the factor governing the number of

persons who would receive water containing the agent. In the vicinity of the pumping station and principal water main, the flow is chiefly from the river and theoretically the concentration of infective agent surviving the water treatment procedure would be the highest at this point. This could account for the localization of the cases along the principal water mains in the center of the city.

Obviously no factual evidence supporting the spread of the disease in the epidemic by drinking water has been obtained. However, this possibility cannot be excluded in view of the lack of evidence supporting other methods of transmission. The fact that the epidemic did not assume the explosive form characteristic of typical epidemics due to water or food-borne agents is not against the possibility in view of the variations in the epidemic pattern that could occur from intermittent contamination of water with the infective agent, the effects of the water treatment procedure on the concentration and activity of the agent, and the influence of concentration and activity of the agent on the incidence and incubation period of the disease.

SUMMARY

An epidemiological investigation of an epidemic of infectious hepatitis that occurred in an industrial city was conducted. At least 52 cases occurred and it is probable that there were additional cases that were unrecognized or not recorded. The distribution of cases in respect to time and location could not be satisfactorily explained by transmission of the causative agent through food, milk, air, fomites, direct or indirect contact, insects and vermin. The only factor common to all cases was the water supply.

In view of the recent reports of transmission of the hepatitis agent by water and its apparent resistance to certain methods used for the disinfection of water, it seems possible that the agent responsible for the described epidemic may have been water-borne. However, no conclusive evidence in support of this or other methods of transmission was obtained by this investigation.

This investigation demonstrates the fact that an epidemic of an unreportable disease such as infectious hepatitis may occur within a city without the knowledge of the public health authorities. As the illness can be of considerable importance to public health, attention is drawn to the desirability of making infectious hepatitis a reportable disease.

CONCLUSIONS

(1) The epidemiology of infectious hepatitis is not yet fully understood. Facts concerning an epidemic are presented with the hope of adding to the knowledge concerning the disease.

(2) All possible sources of infection were investigated but none seemed to be of any importance except for cross infection and the water supply.

(3) Cross infection could not readily explain many of the cases, particularly those occurring simultaneously at widely separated points.

(4) The source of drinking water is not infrequently contaminated by raw sewage.

(5) A rather close relationship of the cases to the pumping station and principal water main was observed. It is in this area that the concentration of the infective agent would be greatest.

(6) The evidence points to the possibility that this epidemic was spread by contaminated drinking water.

(7) The disease should be made reportable as minor outbreaks may pass unnoticed.

Acknowledgment. The author wishes to express his thanks to Dr. T. Grier Miller and Capt. John R. Neefe, MC, AUS, for their invaluable suggestions concerning the conduct of this investigation and their aid in the interpretation of the results.

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CHRONIC GASTRITIS: OBSERVATIONS ON ITS COURSE AND SIGNIFICANCE

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INTRODUCTION

Chronic gastritis has been estimated to occur in three per cent of the general population (1). The cause is unknown; symptoms are obscure or absent; the relationship to peptic ulcer, pernicious anemia and gastric carcinoma is not clearly established, and the consequences of gastritis existing for a prolonged period are conjectural. The purpose of this paper is to report the changes observed gastroscopically in the stomachs of 14 patients repeatedly examined, for periods ranging from eight months to eleven years, in an effort to determine the course, significance and consequence of the inflammatory processes.

Robertson (2) in discussing the pathogenesis of chronic gastritis emphasizes the role of hemorrhage from the capillary vessels with resultant necrosis and subsequent incomplete healing. Layne and Bergh (3) found no alteration in the acid secretion or mucosal appearance after ligation of part of the gastric blood supply in dogs, and also remarked upon the absence of mucosal erosions, ulcerations and hemorrhages in these animals. Devascularization of the greater curvature resulted in no detectable gross or microscopic mucosal damage but ligation of the four large arteries produced death in 36 hours.

Faber (4) contends that gastritis starts early in the life of an individual and results from direct repeated injuries to the gastric mucosa from hematogenous toxins and infections present. These inflammatory changes may progress for years with periods of quiescence, but become progressively worse with time. In later decades the process is sufficiently severe to interfere with the normal function of the mucosa. Secretory disturbances and symptoms may then occur. Faber further suggests that diffuse pangastritis exhibits a characteristic tendency to atrophy without going through the stages of erosive gastritis. On the other hand erosive gastritis may retain its special character for decades without atrophic change. The metaplastic metamorphosis of the glandular structures occurring in long standing gastritis results from the destruction of the normal glands by the inflammatory process.

Faber notes the presence of anacidity in many patients with deficiency diets and attributes it to gastritis. In keeping with this thought is the observation of Sharpless (5) that rats, fed diets low in protein and high in fat, develop mucosal changes of proliferation and ulceration while other investigators (6) have demonstrated recurrent necrosis, hemorrhagic erosions and hemorrhage

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under such conditions. Del Solar et al. (7) report a patient with marked diarrhea and malnutrition and, on x-ray, a filling defect of the lower portion of the stomach suggesting neoplasm. Gastroscopy disclosed narrowing of the distal portion. Disappearance of the lesion, as confirmed by x-ray, was noted after an adequate dietary regimen. The patient later died with pulmonary tuberculosis; severe hypertrophic gastritis in addition to the lung lesion was found at the post mortem examination.

Pollard and Stuart (8) discuss the role of allergy as a factor in the formation of certain forms of gastritis and refer to the experimental work of Afendulis and Gulzow wherein dogs sensitized with horse serum developed swelling and hyperemia of the gastric mucosa following reinjection with this substance. They observed on gastroscopic examination of patients previously found to be normal a succulent mucosa with hyperemia and a lumpy contour of the lesser curvature after the administration of the offending agent. Carey (9), however, observed in dogs, after feeding, a hyperemia and engorgement of the gastric mucosa simulating mild superficial gastritis.

Wolf and Wolff (10) in a study of the effect of emotion on the gastric mucosa noted pallor and decrease in acid secretion in periods of fear and depression while hyperemia and engorgement with increased volume and acidity of the secretion was found in hostility and anxiety states. This hyperemic engorged surface is readily susceptible to injury and conceivably predisposes to the development and persistence of erosions and secondary inflammation. Undue and prolonged acceleration of the hydrochloric acid secretion may result in a similar change. Wolf and Wolff consider the altered gastric function to be a part of the whole pattern of bodily reaction, which when sustained may lead to alteration in structure with gastritis as one of the sequelae.

The multiplicity of possible factors (11) and the many postulated etiologic agents clearly suggest that no one cause is well established. Since the advent of the flexible gastroscope and the introduction of a working classification of gastritis, on the basis of the gastroscopic picture, some progress has been made in the understanding of the condition. The interpretation of the gastroscopic findings is not always easy as variations in the appearance of the gastric mucosa noted with repeated examinations of the same stomach are extremely frequent. The reasons for these changes are not clear, their significance cannot be easily determined and their prognostic import is difficult to evaluate. Physiologic, emotional, physical and chemical influences seem hopelessly interwoven.

Studies correlating the clinical findings, the gastroscopic appearance and the histologic appearance of the mucosa are relatively few. In examinations of biopsies taken from 52, previously gastroscopied, stomachs without the use of clamps or ligatures Schindler and Ortmayer (12) found the gastroscopic and

microscopic interpretation of gastritis to be in agreement. The per cent of accord in the total group, however, was not stated. Swalm and Morrison (13) concluded that the histologic picture agreed with the gastroscopic in 52 per cent of their 25 biopsied cases. Gastroscoically severe gastritis was verified by the histologic examination but mild changes were usually contradicted by the histologic examination. Benedict and Mallory (14) found complete agreement in the correlation of the gastroscopic and microscopic findings in 54.9 per cent of their cases while partial agreement was noted in 33.3 per cent. Contrariwise Maher, Zinninger, Schiff and Shapiro (15) found that "in 28 patients with peptic ulcer examined gastroscopically the mucosa appeared normal in 12, superficial gastritis was present in 10 and either hypertrophic gastritis or hypertrophic and superficial gastritis was present in six. At autopsy or resection within one month after gastroscopy, histological evidence of atrophic gastritis was found in all of the 12 cases which were normal at gastroscopy and in 13 of the remaining 16. This discrepancy may be explained, in part, by the presence microscopically of a certain degree of atrophic gastritis in the so-called normal stomach and by the masking of atrophic changes by superficial or hypertrophic gastritis."

In a comparison of the incidence of the various types of gastritis gastroscopically, Ruffin (16) noted the following dissimilarity between his own and Schindler's observations. (The former examined patients in the North Carolina and while the latter's group were in largely the vicinity of Chicago.)

	NO. CASES	NORMAL	ATROPHIC	SUPERFICIAL	HYPER-TROPHIC
Schindler.....	1200	22.2%	13.6%	11%	17.2%
Ruffin.....	543	63%	9%	1%	2%

These figures indicate a lack in uniformity in the interpretation of the degree and type of inflammation.

OBSERVATIONS

The present paper deals with 14 patients ten of whom were under continued observation because of gastric ulcer. The observations of the gastric mucosa were incidental. However, the patients with ulcer did not appear different from those without ulcer in any respect, except for the ulcer. The presence of the ulcer afforded an excellent basis for repeated gastroscopic examinations and for maintaining the patient under continued observation. For the sake of convenience, the 14 patients have been divided into three groups:

Group 1 consists of two patients with essentially normal findings, one gastroscopied four times in seven months, the other 24 times in seven years.

Group 2 (cases 3 to 10) comprises seven patients with superficial and hypertrophic changes. Case three was examined 100 times in $9\frac{1}{2}$ years; case four, 11 times in eight years; case five, 20 times in four years; case six, 61 times in $8\frac{1}{2}$ years; case seven, 38 times in 11 years; case eight, 8 times in two years and case nine, 81 times in $9\frac{1}{2}$ years.

Group 3 (cases 10 through 14) includes five patients, three of whom exhibited the changes of hypertrophic and superficial gastritis followed later by the prolonged presence of atrophy; in two atrophic gastritis was present from the time of the initial examination. Case ten was gastroscopied 29 times in eight years; case eleven, 7 times in four years; case twelve, 10 times in three years; case thirteen, 19 times in five years; and case fourteen, 6 times in six years.

The majority of the patients were under observation for persistent or recurrent gastric ulcer. The changes were arbitrarily related to the upper, middle and lower thirds (Depths III, II and I respectively) of the stomach and were

TABLE 1

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY
8-27-43	Purpuric areas	Slight	Entire stomach	8 mm. ulcer of lesser curvature
9-10-43	None			Decrease in ulcer size
1-15-44	None			Decrease in ulcer size
2-23-44	Superficial	Slight	Lower third	Irregular edematous tissue in ulcer area

further classified according to their intensity as slight, moderate and severe. The classification of Schindler was used. Each patient was gastroscopied by two or more examiners during the period of observation.

Group 1. Normal Gastroscopic Findings

Case 1, Unit #315439, A. T., white, female, aged 50, was examined four times in seven months, during the gradual disappearance of a gastric ulcer. No changes were noted in the gastric mucosa except around the ulcer. The only symptoms present were those attributable to the ulcer (table 1).

Case 2, Unit #128963, L. B. (28), white female, aged 47 years, at the time of admission was observed over a period of seven years with 24 examinations. A slow growing carcinoma was studied for four and one half years before subtotal resection. During this period 15 of 21 examinations revealed a normal mucosa. The changes noted in the other six examinations were very minor. A slight postoperative inflammation was noted at the 22d examination but at the next examination eight months later, the mucosa was normal. Fullness and epigastric discomfort were prominent symptoms but could not be correlated with either the ulcer or the gastritis (table 2).

Discussion of Group 1. These cases demonstrate the continued presence of a normal mucosa through many examination. This is particularly surprising in

TABLE 2

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY
10-17-38	None	None		Ulcer at angulus probably malignant
11- 7-38	Hypertrophic around ulcer	Slight		
11-19-38	None	Slight		Ulcer, benign
12-13-38	Slight atrophy around ulcer	None		Ulcer, probably malignant
12-23-38	None	None		Ulcer, unusual, benign
3- 3-39	None	None		Ulcer, benign
4-24-39	None	None		Cannot differentiate between carcinoma and hypertrophic ulcerative gastritis
6-22-39	Erosions around the ulcer	None		Ulcer suggestive of benign lesion
7-24-39	None			Ulcer, evidently benign
8-21-39	None	None		Ulcer, benign
9-27-39	Hypertrophic changes around ulcer	Moderate	Lower third	Ulcer, if seen for the first time would consider neoplasm
10-27-39	None	None		Ulcer, definitely benign
12- 6-39	None	None		Ulcer, atypical, suggests neoplasm
3-13-40	None	None		Ulcer, unusual unfamiliar changes
4-17-40	Atrophic	Slight	Middle portion	Ulcer, apparently benign
5-29-40	Hypertrophic	Slight	Middle portion	Ulcer, benign
6-26-40	None	None		Benign ulcer with crater
8- 8-40	None	None		Benign ulcer
3- 3-41	None	None		"Question of benign ulcer or cancer"
6-25-41	None	None		Carcinoma
3-25-42	None	None		"Unusual lesion suspect malignancy"
4-16-43	Post-operative gastritis	Slight	Middle portion	
11-12-43	Normal post-operative stomach	None		
7-25-45	Normal post-operative stomach	None		

Case 2, a rather marked psychoneurotic. Perhaps hostility and anxiety were not sufficiently prominent features of her neurosis.

Group II. Superficial and Hypertrophic Changes

Case 3 (29), Unit #144032, W. G., male, white, aged 46, on admission with a chronic recurrent gastric ulcer was examined 100 times during almost a decade. The initial observation revealed a mild hypertrophic gastritis of the lower stomach which continued for 18 months, being visualized on ten occasions. X-ray therapy was then administered in an effort to decrease the acid secretion. In the following three years thirty examinations disclosed, with few exceptions, the presence of a severe superficial gastritis. In the fifth and sixth years severe hypertrophic changes were present while 40 gastroscopies during the sixth through the ninth years disclosed superficial

TABLE 3

GASTROSCOPIES	DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl	COMMENT
1	1-20-36	Hypertrophic	Mild	Lower third	Gastric ulcer, benign	44	Following x-ray therapy
10	6- 2-37	Hypertrophic	Mild	Lower third	Ulcer, healed	110	
20	2- 9-38	Superficial	Severe	Diffuse	No ulcer seen	60	
30	10- 5-38	Superficial	Slight	Middle third	Small ulcer with surrounding inflammation	70	
40	7-14-39	Superficial	Severe	Diffuse	Shallow ulcer	39	
50	7- 8-40	Hypertrophic hemorrhagic	Severe	Lower third	Ulcer	59	
60	5-14-41	Hypertrophic	Moderate	Upper third	1 cm. ulcer		
70	3-20-42	Superficial	Mild	Middle third	Ulcer, 5 mm.		
80	3-22-43	Superficial	Mild	Middle third		58	
90	8-21-44	Superficial	Mild	Upper two-thirds	Ulcer	45	
100	11-15-45	Superficial	Mild	Upper two-thirds	Ulcer, 3 mm.		

gastritis changing from severe to moderate to mild in a two year period and remaining mild during the ensuing three years. During the first four years the lower stomach was principally involved whereas the upper half was the chief site of change during the latter part of the observation. No atrophic changes were noted at any time. At many examinations, though the patient had only slight gastro-intestinal complaints gastroscopy revealed a gastric ulcer and a changing mucosal picture (table 3).

Case 4, Unit #293108, J. W., white, male, aged 62 years, at the time of admission in 1942 was found to have a gastric ulcer near the site of a previous gastroenterostomy. He was placed on medical management consisting of a Sippy regimen and was followed for two years. Because of the persistence of the stomal ulcer bilateral vagotomy was done. During this two year interval eleven gastroscopies disclosed super-

ficial changes in the middle portion of the stomach in addition to the stomal ulcer. At the last examination, prior to vagotomy, severe hypertrophic erosive gastritis was noted. One month after vagotomy, gastroscopy disclosed slight superficial change (table 4).

Case 5, Unit # 260933, J. A., white, male, aged 41 years, at the time of admission with a gastric ulcer was examined 20 times in four years. A normal mucosa was seen at the first examination; severe diffuse hypertrophic changes, involving the lower two thirds of the stomach were noted twice during the next thirty days. The latter examinations followed x-ray therapy. One month later slight superficial gastritis was noted. In the following year, three examinations were done, the second revealing moderate hypertrophic change, the first and third normal findings. The ulcer then recurred and bilateral vagotomy was done. During the next two years six gastroscopies showed slight to moderate superficial change. Severe superficial erosive

TABLE 4

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	COMMENT
10-26-42	Purpuric spot	Slight	Middle portion	Ulcer not visualized	
2-12-43	Superficial	Slight	Middle portion		
8-30-43	Superficial	Slight	Diffuse	Ulcer	
9-24-43	Superficial	Slight	Middle portion	Ulcer	
11-19-43	Superficial	Slight	Middle portion	Ulcer	
3-22-44	Superficial	Slight	Middle portion	Ulcer	
4-24-44	Superficial	Slight	Middle portion	Ulcer	X-ray therapy
5-24-44	Superficial	Slight	Middle portion	Ulcer	
7-26-44	Superficial	Slight	Middle portion	Ulcer healed	
11-13-44	Hypertrophic hemorrhagic erosive	Severe	Middle portion	Ulcer recurred	Vagotomy 11-27-44
12-11-44	Superficial	Slight	Diffuse		

gastritis was noted at the last examination but the gastric ulcer did not recur. Hypertrophic changes were not found after vagotomy. Recurrent attacks of ulcer distress were noted with the reappearance of the ulcer. When gastroscopy revealed only superficial and hypertrophic gastritis, indefinite symptoms were at times present; at other times there were none (table 5).

Case 6, Unit # 165135, M. N., white, female, aged 63 years at the time of admission with a recurrent lesser curvature ulcer was under observation for eight and one half years. Sixty-one gastroscopic examinations during the first five years disclosed hypertrophic changes, normal mucosa, superficial gastritis, atrophic gastritis for a prolonged period, then atrophic combined with superficial gastritis. All of the changes were slight to moderate in severity. The hypertrophic process chiefly involved the lower part of the stomach while the atrophic changes were in the upper portion. After the first five year period, there was an interval of 30 months during which nine gastroscopies disclosed a relatively normal mucosa. During the next year moderate atrophic and superficial changes were noted at three examinations: There was no

apparent relationship between the ulcer, the appearance of the gastric mucosa and the symptoms (table 6).

TABLE 5

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl	COMMENT
4-16-41	Normal			Ulcer—small erosion		
4-30-41	Hypertrophic	Severe	Lower two thirds	Ulcer—small erosions	53	X-ray therapy
5- 7-41	Hypertrophic	Severe	Diffuse	Ulcer decreased		
6- 2-41	Hypertrophic	Moderate	Lower two thirds	Hemorrhagic erosions		
7-18-41	Superficial	Slight	Lower two thirds	Hemorrhages slight	39	
11- 5-41	Normal			Slight inflammation around recurrent ulcer	100	
11-17-41	Normal		Upper one third	Purpuric spots		
12- 3-41	Normal		Middle one third	Ulceration in region of ulcer		
12-31-41	Superficial hypertrophic	Slight	Middle one third			
1-19-42	Normal			Sanguinous secretion middle one third		
4-3 -42	Hypertrophic ulcerative	Moderate	Middle one third			
10-30-42	Normal					
1-22-43	Hypertrophic	Slight	Middle one third			
6-21-43	Hypertrophic	Moderate	Upper two thirds	Ulcer recurred	88	Vagotomy
10-27-43	Superficial	Moderate	Lower one third			
3-27-44	Normal			Gastric purpura slight		
6- 5-44	Superficial	Moderate	Diffuse			
8- 7-44	Superficial	Moderate	Middle one third			
11- 6-44	Superficial	Slight	Lower two thirds		28	
5- 3-45	Superficial erosive	Severe	Diffuse			

Case 7 (30), Unit #70208, R. F., white, male, aged 42 years, at the time of admission was observed over a period of 11 years with 38 examinations. During this

TABLE 6

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
1- 6-37	Hypertrophic	Moderate	Upper one third	Ulcer, benign?	
1-24-37	Hypertrophic	Slight	Upper one third	Ulcer	
2- 3-37	Hypertrophic erosive	Moderate	Upper one third	Ulcer, healing	
2-24-37	Normal			Ulcer not visible	
3-24-37	Hypertrophic	Slight	Lower one third		
4- 7-37	Normal			No ulcer	
5-19-37	Hypertrophic	Slight	Upper one third	No ulcer	
6-16-37	Hypertrophic	Slight	Upper one third	Shallow radiating folds in ulcer area	
11- 3-37	Hypertrophic	Slight	Lower one third	No ulcer	
1- 5-38	Atrophic	Severe	Diffuse	Ulcer scar	
3-30-38	Normal			Ulcer scar mucosal hemorrhages	10
6-27-38	Hypertrophic	Slight	Upper one third	Distortion of antrum and pylorus	20
10-22-38	Hypertrophic	Slight	Upper one third	1.5 cm. ulcer lesser curvature	15
11-16-38	Normal			Healing ulcer	20
12- 9-38	Normal			Healed ulcer	
1-12-39	Hypertrophic	Slight	Upper one third	Healed ulcer	15
3- 3-39	Superficial atrophic	Moderate	Upper two thirds	8 mm. shallow benign ulcer distant from old ulcer area	
3-15-39	Atrophic	Moderate	Upper one third	Ulceration of middle lesser curvature, healing	0
4- 5-39	Atrophic	Moderate	Upper one third	Ulcer healed	0
4-19-39	Atrophic	Moderate	Upper one third	3 mm. ulceration lesser curvature	5
4-24-39	Superficial with atrophic	Moderate	Diffuse—upper two thirds	No ulcer	17
7-28-39	Superficial	Moderate	Lower one third		
7-28-39	Atrophic and hypertrophic	Moderate	Upper two thirds	No ulcer	
8-30-39	Atrophic and superficial	Moderate	Diffuse	No ulcer or scar	
9-27-39	Patchy atrophic	Moderate	Upper two thirds	Erosion?	
10-27-39	Atrophic	Moderate	Middle third	Shallow ulcer	
11-15-39	Superficial	Slight	Lower one third	Shallow ulcer	64
12-22-39	Superficial erosive	Moderate	Middle third	Shallow ulceration	
1-26-40	Atrophic	Slight	Upper one third		
2-10-40	Superficial atrophic	Severe moderate	Middle one third	Shallow ulceration middle lesser curvature	
2-26-40	Superficial atrophic patchy	Moderate moderate	Lower one third upper two thirds		40
3-11-40	Superficial atrophic	Moderate moderate	Diffuse upper one third	No ulcer	0

TABLE 6—Continued

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
3-27-40	Atrophic	Slight	Upper one third	No ulcer	
4-12-40	Normal				0
5-22-40	Hypertrophic hemorrhagic atrophic	Moderate moderate	Lower one third upper one third	No ulcer	11
6-28-40	Atrophic patchy superficial	Moderate moderate	Diffuse	No ulcer?	
7-26-40	Atrophic	Moderate	Upper one third		
9-20-40	Atrophic	Moderate	Upper one third	Shallow, 5 mm. ulcer of angulus	17
10-25-40	Superficial	Slight	Middle one third	4 mm. ulcer	
1-10-41	Hypertrophic	Severe	Upper one third	Ulcer not visualized	44
2-21-41	Superficial	Moderate	Lower one third	Ulcer not visualized	
3-21-41	Superficial	Slight	Middle one third	Two small mucosal hemorrhages	22
4-25-41	Superficial	Slight	Middle one third	4 small hemorrhages	
6-13-41	Atrophic	Slight	Lower one third	No ulcer	
7-11-41	Atrophic with hemorrhagic features	Severe	Upper one third		31
7-25-41	Atrophic	Moderate	Upper one third	No ulcer	
10-10-41	Atrophic	Moderate	Upper one third	Purpura, moderate	28
11-14-41	Atrophic hemor- rhagic	Moderate	Upper one third	Purpura, moderate	29
1-16-42	Normal			Small ulcer in a different site	
3-20-42	Superficial	Slight	Middle one third	Small ulcer	
4-17-42	Superficial	Slight	Middle third	Shallow small erosion	25
5-15-42	Normal			Small ulcer with swelling around the ulcer	0
8-21-42	Normal			No ulcer	
1- 6-43	Normal			Ulcer scar	
1-22-43	Normal			Ulcer scar, swelling around the scar	
6-23-43	Hypertrophic	Slight	Lower one third		
3- 3-44	Normal			No ulcer	
7-10-44	Normal				
11-10-44	Atrophic	Moderate	Upper one third	No ulcer	0
3- 9-45	Atrophic	Moderate	Upper one third	No ulcer	0
6- 8-45	Superficial	Moderate	Diffuse		
11-23-45	Atrophic	Slight	Lower two thirds upper one third	None	

time slight, moderate, or severe changes were noted without any determined relationship to each other. The lower two thirds of the stomach was involved more than the upper third. Superficial or hypertrophic changes were noted at each examination; yet the severity was about the same in the later years of observation as it was

TABLE 7

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
11-12-34	Superficial	Moderate	Upper one half	None	
9-23-36	Hypertrophic	Moderate	Diffuse	None	
10-27-37	Hypertrophic erosive	Moderate	Lower one half		
6-22-38	Superficial	Severe	Upper one half	None	50
10-17-38	Superficial	Moderate	Diffuse	Shallow gastric ulcer	50
11-19-38	Superficial	Moderate	Diffuse	Shallow gastric ulcer	30
12-19-38	Hypertrophic	Severe	Diffuse	Ulcerations, superficial	
1-19-39	Superficial	Moderate	Diffuse	None	94
3-17-39	Hypertrophic	Moderate	Diffuse	Shallow ulcerations	
6-19-39	Hypertrophic	Moderate	Lower one half	Ulcerations, shallow	
8-21-39	Hypertrophic	Moderate	Lower one half	Small shallow ulceration	
10- 2-39	Hypertrophic	Moderate	Lower one half	Ulcerations	
12- 4-39	Hypertrophic	Moderate	Lower one half	Ulcerations	
2- 7-40	Superficial	Moderate	Diffuse		
4- 8-40	Superficial	Severe	Lower one half		19
7-22-40	Healed hypertrophic	Slight	Lower one half	Ulcerations absent	
9-11-40	Hypertrophic	Slight	Lower one half	None	
11-13-40	Superficial atrophic	Severe moderate	Lower one half upper one half	None	
2-17-41	Superficial	Severe	Lower one half	None	
6-23-41	Normal	Normal		Ulcer at angulus	
7-14-41	Hypertrophic	Mild	Lower one half	Ulcer at angulus	
9- 3-41	Hypertrophic superficial	Moderate moderate	Lower one half upper one third	None	
9-15-41	Hypertrophic superficial	Moderate severe	Middle one third upper one third	None	
11-10-41	Hypertrophic	Severe	Middle one third	Ulcerations	
12- 1-41	Hypertrophic	Severe	Middle one third	Ulcerations	
1-19-42	Hypertrophic superficial	Moderate moderate	Lower one third upper one third	None	
3-13-42	Hypertrophic	Severe	Lower one third	Ulcerations	
7-29-42	Hypertrophic	Severe	Middle one third	None	
11-30-42	Hypertrophic	Moderate	Middle one third	None	22
9-29-43	Superficial	Moderate	Diffuse	Erosions	
12-29-43	Superficial	Mild	Diffuse	None	
4- 5-44	Superficial	Mild	Lower one half	Ulcer at angulus	
5-24-44	Superficial	Mild	Lower one half	Ulcer present	
8- 9-44	Superficial	Moderate	Lower one half	None	
12- 6-44	Superficial	Severe	Diffuse	None	
3-26-45	Superficial	Moderate	Diffuse	None	
6-25-45	Superficial	Slight	Middle one third	Slight atrophy	
10- 2-45	Superficial	Moderate	Diffuse	Slight atrophy	33

earlier. This case illustrates the chronicity of gastritis, and raises again the question of the relationship of the hypertrophic and superficial forms. The frequent transition from one to the other suggests that the two may be variants of the same process. No correlation between the gastroscopic findings and the clinical course of the patient has been noted. During periods of moderate and severe gastritis, gastroscopically, the patient had no subjective complaints (table 7).

Case 8, Unit #319720, A. H., white, male aged 32 years at the time of admission was treated for an irritable colon and psychoneurosis. In the course of two years eight gastroscopic examinations were performed. At first an erosive hemorrhagic gastritis lasting three months was observed. During the next year the stomach was examined three times and found normal. Six months later, two years after the initial examination a severe hypertrophic hemorrhagic gastritis was noted. This is an example of erosive hemorrhagic gastritis of moderate degree with healing and recurrence

TABLE 8

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
11-23-43	Erosive hemor-rhagic	Moderate	Middle stomach	None	64
2- 2-44	Erosive hemor-rhagic	Slight	Middle stomach		
4-24-44	Hypertrophic hem-orrhagic erosive	Slight	Middle stomach cardiac portion		
7-26-44	None		Normal stomach		
2-28-45	None		Normal		
5-23-45	None		Normal		
10-31-45	Hypertrophic hem-orrhagic erosive	Severe	Cardiac		0
12-14-45	Hypertrophic su-perficial	Moderate moderate	Upper two thirds		58

after 15 months. This patient complained of recurrent upper abdominal distress with a normal mucosa as well as when inflammatory change was present (table 8).

Case 9, Unit #148736, A. K., (29), white, female, aged 63 years at the time of admission because of a recurrent chronic gastric ulcer was examined 81 times during a 9½ year period. Mild superficial changes alternating with normal findings were present at 18 examinations in the first two years. During the next three years 40 examinations revealed a predominantly normal mucosa with occasional mild superficial change. A slight increase in the incidence of superficial change was noted in 23 examinations in the following four and one half years. Again the normal and abnormal states of the mucosa fluctuated in a totally unpredictable and unrelated manner. At times a small superficial ulcer was visualized by gastroscopy but the patient's symptoms rarely corresponded with it or with the state of the mucosa (table 9).

TABLE 9

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
4-17-36	Erosion	Mild	Upper one third	Gastric ulcer	
5-27-36	Superficial	Mild	Middle portion	Gastric ulcer, almost healed	
6-17-36	Superficial	Mild	Middle portion	Gastric ulcer, healing	
7-17-36	Superficial	Severe	Lower two thirds	Gastric ulcer, chronic	25
8- 5-36	Normal			Gastric ulcer	
10-28-36	Normal			Gastric ulcer	
12-10-36	Superficial	Slight	Upper one third	Ulcer scar	
3-17-37	No comment on the mucosa			Gastric ulcer, healing	
4-14-37	No comment on the mucosa			Small erosion at site of former ulcer	
5-12-37	Erosions	Slight	Upper one third	4 mm. ulcer	
6-23-37	Hypertrophic	Moderate	Middle one third	Slight increase in diameter	
9- 1-37	No comment on the gastritis			Ulcer 1 cm. in diameter	
12- 2-37	Atrophic	Slight	Lower one third	Small benign ulcer beginning hour glass stomach	
1- 5-38	Hypertrophic	Slight	Lower one third	Small shallow ulcer	50
2- 9-38	Normal			Few erosions, healed ulcer	
2-28-38	Normal			Healed ulcer, few mucosal hemorrhages	
3-10-38	Normal			No ulcer	
3-29-38	Normal			Slight hemorrhages of normal mucosa first stage of hour glass stomach	
7- 6-38	Hypertrophic	Slight	Middle one third	Recurrent ulcer mucosal hemorrhages slight	50
8- 5-38	Normal			Recurrent ulcer beginning hour glass formation	
8-26-38	Normal			Ulcer (shallow) with mucosal hemorrhages	25
11-19-38	Normal			Small ulcer and mucosal hemorrhages	50
12-12-38	Normal			Erosions around ulcer (superficial)	
1- 6-39	Atrophic	Slight	Middle one third	Ulcer almost healed	

TABLE 9—Continued

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
1-27-39	Normal	Slight	Middle one third	Ulcer healed slight mucosal hemorrhages	56
2-24-39	Normal			2 ulcers in old ulcer area	
3-24-39	Superficial		Middle one third	Large ulcer crater	
3-27-39	Normal			Ulcer with slight hemorrhages	30
4- 3-39	Normal			Shallow ulcer	
4-17-39	Normal	Slight		Smaller ulcer	
6-23-39	Normal			Ulcer unchanged	35
7-14-39	Normal			Ulcer unchanged	
10- 2-39	Superficial		Middle one third	Ulcer 5 cm. below cardia	
10-23-39	Normal			Ulcer 1.5 cm. in diameter	
11- 3-39	Superficial	Slight	Upper one third	Ulcer, as before	20
12- 1-39	Normal			Ulcer healed	0
12- 6-39	Normal			Ulcer scar with converging folds	
1-19-40	Normal	Slight		Ulcer healed	0
2-16-40	Normal			Small ulcer in old scar	
3- 1-40	Normal			Healing ulcer	32
3-15-40	Normal			Ulcer crater deeper	
3-29-40	Superficial		Middle one third	Ulcer still present	
4-12-40	Normal			Very shallow ulcer small mucosal hemorrhages	24
5-17-40	Normal			3 mm. ulcer	
6-21-40	Normal			Shallow ulcer	32
7-15-40	Normal			Shallow ulcer	
8-26-40	Normal			Ulcer 1.5 cm. in diameter	
10- 7-40	Normal			Ulcer unchanged	
11-18-40	Normal			Ulcer smaller	
1- 6-41	Hypertrophic	Mild	Middle portion	Ulcer, almost healed	31
2- 3-41	Hypertrophic	Mild	Middle portion	5 mm. ulcer	
3-10-41	Normal			7 mm. ulcer	
4- 7-41	Swelling of mucosa around ulcer		Middle portion	Ulcer	
4-28-41	Normal			Ulcer present	32
5-12-41	Normal			Ulcer	
6- 2-41	No comment on mucosa			Ulcer unchanged	
6-30-41	Normal			Ulcer 3 mm. in diameter	

TABLE 9—*Continued*

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
8-25-41	Superficial	Mild	Middle portion	Mucosal hemor- rhages, ulcer healed	0
10- 3-41	Atrophic	Mild	Lower one third	Shallow ulcer	13
10-17-41	Normal			3 mm. ulcer	
11-10-41	Normal			Healed ulcer	
2-20-42	Normal			Ulcer deeper	
3-20-42	Superficial	Slight	Middle portion	Ulcer slightly deeper	38
4-17-42	Superficial	Slight	Middle portion	Ulcer as before	
5-15-42	Superficial	Slight	Middle portion	Ulcer healed	
10-28-42	Normal			1.3 cm. ulcer with hour glass fold	36
1-22-43	Normal			Ulcer healed, hour glass fold	
2-19-43	Superficial	Slight	Middle portion	3 mm. ulcer, re- current	0
3-19-43	Superficial	Slight	Middle portion	Ulcer unchanged	
5- 6-43	Superficial with hemorrhagic spots	Slight	Middle portion	Ulcer unchanged	
5-14-43				Ulcer	31
6- 4-43	Redness of tissue around ulcer	Slight	Middle portion	Ulcer decreased 1 mm. in diameter	
10-29-43	No mention of mucosa			1 mm. ulcer	15
12-10-43	Normal			Ulcer not visu- alized	
1-21-44	Superficial		Lower one third		15
4-21-44	Normal			Ulcer, 3 mm.	
9-15-44	Normal			Shallow ulcer	
3-16-45	Normal			3 mm. ulcer	
5-11-45	Hypertrophic	Slight	Middle portion	No ulcer seen	
8-10-45	Superficial	Moderate	Lower two thirds	No ulcer visualized	
11- 9-45	Superficial	Slight	Lower two thirds	None	

Summary of Group 2. In Case 3 we followed the course of gastritis over a ten year period. In the first four years hypertrophic gastritis is succeeded by the superficial type which returns to the hypertrophic phase during the next two years and is followed by superficial inflammation during the last four. No atrophy was noted at any time.

Case 4 demonstrates slight superficial gastritis unchanged after vagotomy although the gastric ulcer, previously present, disappeared.

Case 5 illustrates the manner in which hypertrophic and superficial gastritis and a perfectly normal mucosa may alternate in an unpredictable manner. Following vagotomy only superficial gastritis was present.

Case 6 likewise shows the unpredictable transitions in the phases or types of gastritis over a span of eight and one half years.

In Case 7, as in Cases 5 and 6, moderate to severe superficial and hypertrophic changes were found over 11 years.

Case 8. This case illustrates healing with a recurrence of severe erosive gastritis.

Case 9. Recurring mild superficial gastritis and at other times mild hypertrophic gastritis were noted in 81 examinations during nine and a half years, but in 44 of the examinations the mucosa was normal.

Discussion of Group 2. Carey (17) suggests that hypertrophic gastritis, may be a phase in the regenerative process with proliferation of the surface epithelium and replacement by non-specific columnar epithelium of the specific gland structures, and lymphocytic infiltration. Hypertrophic changes were noted in 22.5 per cent of 700 gastroscopies whereas Ruffin (16, 18) finding only 2 per cent in 543 examinations considers hypertrophic gastritis to be relatively unimportant.

The thickness of gastric mucosa is subject to marked variation, but seems related to the number of secreting cells present (19). Tanner (20) thinks that mild inflammatory change occurring in a thick mucosa and seen gastroscopically from a close up oblique view may be falsely diagnosed as hypertrophic gastritis because of the distorted appearance (21). Gill studied, gastroscopically, the response of the stomach to insulin and histamine. The highest concentration of free HCl and the greatest amount of secretion per minute was noted in hypertrophic gastritis. This suggests, since it is unusual to associate inflammation with enhanced function, that some forms of hypertrophic gastritis represent merely physiologically hyperactive mucosae. Jones (21) speaks of a thick "pebbled beach" appearing mucosa without demonstrable inflammation which has been called hypertrophic gastritis but is considered by him to be a constitutional change only. When it is associated with inflammation, the nodular changes are much more irregular with patchy hyperemia and an excess of mucus. Schindler (22) stresses the dull, loose spongy consistency of the mucosa with diminution or absence of highlights. "The changes are usually noticed first in the valleys between the folds; later the hypertrophic character is more prominent. Small dark creases are noted through the dull swollen mucosa and granular nodules, larger nodules and big nodes are usually present. The creases and crevasses make up the boundaries of irregular polygonal areas of different sizes which in the earlier stages seem to lie in the same level, but later they become irregularly elevated and of different size. When the mucosal folds are affected they become irregular and are subdivided by perpendicular creases." He points out that the diagnosis of hypertrophic gastritis

cannot be made with certainty in the presence of a spastically contracted stomach and that diffuse hyperemia is not a sign of hypertrophic gastritis, rarely being present. The difficulty in deciding where the normal ends and the abnormal begins is illustrated by Thompson's (21) experience in 1,400 gastroscopic examinations. In the first 300 cases he diagnosed hypertrophic gastritis 18 times (6%) whereas in the last 300 he made the diagnosis only twice (0.66%). Apparently in hypertrophic gastritis particularly the tendency is to diagnose gastritis too frequently and to fail to make allowance for the great normal variations.

Six of the seven cases in this group were found on different and multiple occasions to have superficial gastritis at one time and hypertrophic gastritis on another, thus suggesting not only a close relationship between the two but also the likelihood that they represent variant phases of the same process. The significance of these changes is not apparent. They seem to be rather transitory phenomena with a marked tendency to recur.

Group III. Hypertrophic, Superficial and Atrophic Gastritis

Case 10, Unit # 177205, E. B., white, male, aged 38 years, with a recurrent gastric ulcer was subjected to 29 gastroscopies in 8 years. Slight hypertrophic change of the middle portion of the stomach was found at the initial examination. The patient then received x-ray therapy directed at the gastric fundus in order to reduce the amount of gastric secretion. Two months later the middle stomach was the site of a severe superficial gastritis. This was present in the lower portion for three years varying from moderate to severe at 18 examinations carried out at intervals of two to three months. Atrophic features were then noted in the upper one third in addition to moderate superficial change in the middle portion during the next five year span. Nine gastroscopic examinations confirmed these findings.

This is in accord with Faber's statement that atrophic change may occur in long-standing gastritis and is in agreement with Schindler's conception of atrophic gastritis as a sequela of superficial gastritis (23). No definite correlation of the mucosal variations and the occasional fatigue and nervousness of the patient was noted (table 10).

Case 11, Unit # 243308, B. P., white, female, aged 64 years, with a gastric ulcer was observed four years during which seven gastroscopies were performed. The first revealed severe atrophic gastritis of the upper half of the stomach associated with areas of hemorrhage, confirmed by four succeeding examinations in the next years. Subtotal gastrectomy was carried out because the ulcer continued to recur. Histological examination disclosed in addition to a benign gastric ulcer diffuse atrophic hemorrhagic gastritis and metaplasia to an intestinal type of gland. Gastroscopic examination of the remaining stomach three years later disclosed a normal mucosa. This suggests that an atrophic mucosa, even with severe changes including metaplasia, may return to normal or at least form a normal appearing surface. Epigastric dis-

truss which radiated to the right was the patient's chief complaint. A free acidity of 48 was present in spite of the severe atrophic hemorrhagic gastritis (table 11).

Case 12, Unit #283560, H. A., white, male, aged 43 years, on admission, was

TABLE 10

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl
6-30-37	Hypertrophic	Slight	Middle portion		110
10-15-37	Superficial	Slight	Lower third	(X-ray therapy)	
12- 3-37	Superficial	Severe	Middle portion	Small ulcer	0
1- 5-38	Superficial	Slight	Middle portion	None	
4- 1-38				None	
5-17-38	Superficial	Severe	Diffuse	None	0
6-15-38	Superficial	Moderate	Middle third	None	
7-18-38	Superficial	Severe	Lower third	None	0
10-24-38	Superficial	Severe	Lower third	Henning sign	15
11-19-38	Superficial	Moderate	Lower two thirds	None	10
12-15-38	Superficial	Moderate	Lower third	None	
4-25-39	Superficial	Moderate	Lower third	None	0
6-28-39	Superficial	Severe	Lower third	None	14
9-20-39	Superficial	Severe	Lower third	None	0
10-18-39	Superficial	Severe	Lower third	None	0
12-20-39	Superficial	Severe	Lower third	None	0
3- 1-40	Superficial	Severe	Lower third	None	
5-31-40	Superficial	Moderate	Lower third	None	8
8-23-40	Superficial	Moderate	Lower third	Shallow ulceration	0
9-18-40	Superficial	Moderate	Lower third	None	
1- 6-41	Atrophic	Slight	Upper half	None	
5- 5-41	Superficial devel- oping into atrophic	Moderate	Upper third	None	0
8-11-41	Superficial devel- oping into atrophic	Moderate	Upper third	None	0
11-10-41	Superficial	Moderate	Upper third	None	
3-16-42	Atrophic	Moderate	Upper two thirds	(No superficial gas- tritis noted)	
3- 1-43	Superficial and atrophic	Moderate	Diffuse		0
7-26-44	Superficial atrophic	Moderate mild	Lower two thirds upper third	None	
6- 6-45	Superficial atrophic	Moderate moderate	Lower two thirds upper third	None	0
12- 5-45	Atrophic superficial	Severe mod- erate	Upper two thirds middle portion	None	0

treated over a three year period for a lesser curvature ulcer during which time 10 gastroscopic examinations were done. At the first examination, the ulcer was visualized and the gastric mucosa found normal; the same conditions were present two

months later. X-ray therapy was then given. Sixty days later a slight diffuse atrophy of the mucosa was noted; eighteen months later the stomach was found normal. In the following eight months three examinations were done. The first disclosed diffuse atrophy while the last two showed moderate atrophic change in the upper and lower thirds of the stomach. Two examinations 8 months after this re-

TABLE 11

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	COMMENT
6-20-40	Atrophic	Severe	Upper half	Hemorrhagic areas	Ulcer—not demonstrable by gastroscopy X-ray suggestive of erosive gastritis
7-24-40	Atrophic	Severe	Upper half		
10- 4-40	Atrophic	Severe	Diffuse	Hemorrhagic areas	
2- 6-41	Atrophic	Severe	Diffuse	Hemorrhagic areas	
7-21-41	Atrophic	Severe	Upper half	Hemorrhagic areas	Subtotal gastrectomy
8-15-41	Unsuccessful examination				
8-23-44	None		Normal		

TABLE 12

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl	COMMENT
5- 8-42	None	Slight	Diffuse	Ulcer	79	X-ray therapy
7- 8-42	None			Ulcer	44	
8- 5-42	Atrophic			Ulcer		
2- 4-44	None	Slight	Upper third	Ulcer by x-ray	50	Hour glass stomach
4-28-44	Atrophic					
7-17-44	Atrophic	Moderate	Diffuse			Hour glass constriction
1-19-45	Atrophic superficial	Moderate moderate	Lower third upper third	Ulcer by x-ray	65	Hour glass constriction
3-28-45	Atrophic	Moderate	Upper third			Hour glass constriction
11- 7-45	Superficial	Moderate	Upper third	Ulcer by gastroscopy		Hour glass constriction
12-19-45	Superficial and hypertrophic	Moderate	Upper two thirds	Ulcer by gastroscopy		

vealed moderate superficial change. The patient usually had symptoms when the ulcer was active but it was not possible to relate the symptoms with the state of the mucosa (table 12).

Case 13, Unit #5918, K. A., white, female, aged 44, was observed for five years during which time 19 gastroscopies were performed. Atrophic changes varying from moderate to severe were noted constantly in the upper two thirds of the stomach.

At one examination a nodular appearance suggestive of hyperplasia in an atrophic mucosa was noted, but eight months later there was no evidence of this. Liver ex-

TABLE 13

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCl	COMMENT
8-29-39	Atrophic	Moderate	Cardia	None	0	Ventriculin
11- 8-39	Atrophic	Moderate to severe	Upper two thirds			
12-11-39	Atrophic	Moderate to severe	Upper two thirds			
1- 3-40	Stomach looks almost normal				0	
3- 6-40	Atrophic	Severe	Middle portion		0	
4- 2-40	Atrophic	Severe	Middle portion			
6-17-40	Atrophic	Severe	Upper two thirds			
8- 5-40	Atrophic	Moderate	Upper two thirds			
9-11-40	Atrophic	Slight	Upper one third			After liver therapy
10-23-40	Atrophic	Moderate	Upper one third			
1-10-41	Atrophic	Severe	Upper two thirds			Liver therapy
4- 9-41	Atrophic	Severe	Upper two thirds			
6- 9-41	Atrophic	Severe	Upper two thirds			
9- 8-41	Atrophic	Severe	Upper two thirds			
1- 6-42	Atrophic	Severe	Upper two thirds	Hyperplastic node formation in lower stomach Superficial changes—slight		
8-31-42	Atrophic	Moderate	Middle portion			
1-27-43	Atrophic	Severe	Upper portion			
10-13-43	Atrophic	Severe	Upper two thirds			
7-12-44	Atrophic	Severe	Upper two thirds			

tract and ventriculin had no effect on the atrophy. A multitude of vague complaints associated with fatigue and intermittent diarrhea was noted over the years of obser-

vation. The severity of the gastritis was not reflected in the clinical state. The patient has a severe psychoneurosis (table 13).

Case 14, Unit #217299, A. F., white, male, aged 38 years, with a recurrent prepyloric ulcer was observed intermittently over six years with six gastroscopies. Slight hypertrophic changes of the pars media were noted at the initial examination. This process seemed more severe and more extensive at the time of the third examination made 16 days after x-ray therapy. Six months later this portion of the stomach appeared normal but slight atrophy of the lower third was present; four years later moderate atrophy was found in the lower third. X-ray therapy was again administered, the prepyloric ulcer having recurred; gastroscopy one month later (6th examination) disclosed moderate atrophy of the cardia and antrum. In this case then hypertrophic changes were observed followed in the course of four years by atrophy in

TABLE 14

DATE	TYPE OF GASTRITIS	DEGREE OF INFLAMMATION	LOCATION	ASSOCIATED PATHOLOGY	HCI	COMMENT
4-14-39	Hypertrophic	Slight	Angulus	Duodenal ulcer		
1-10-41	Hypertrophic	Moderate	Middle stomach	Duodenal ulcer	110	
2-13-41 (16 days after x-ray exam)	Hypertrophic	Severe	Middle portion and cardia	Hemorrhagic areas	91	X-ray therapy
8-4-41	Atrophic	Slight	Lower third	Distortion of pylorus	77	
10-1-45	Atrophic	Moderate	Middle third			X-ray therapy
11-5-45 (x-ray therapy from 10-10-45)	Atrophic	Moderate	Diffuse		35	

different portions of the stomach. The fundus, at which the radiation therapy was directed was not involved in the inflammatory process except in the third examination made 16 days after completion of the irradiation. During the years of observation the symptoms were correlated with pyloric obstruction due to an intrapyloric ulcer but not with the appearance of the gastric mucosa (table 14).

Summary of Group 3. Case 10—following x-ray therapy, superficial changes of the stomach were noted for three years, then atrophic changes were observed for five years.

Case 11—persistent severe atrophic gastritis without change confirmed by histologic examinations with apparent return to normal after resection of part of the stomach.

Case 12—on the initial examination the mucosa was normal; following x-ray therapy moderate atrophic change of the lower third was seen over a three year period which was followed by moderate superficial changes after 8 months.

Case 13—marked atrophy of the upper third persisted over five years.

Case 14—following x-ray therapy hypertrophic gastritis of the middle portion of the stomach disappeared; atrophic gastritis developed in the antrum and persisted for four years.

DISCUSSION

In this series of 14 cases with repeated gastroscopic examinations over many years prolonged atrophy was observed in five. In two, superficial and hypertrophic changes were followed by atrophy, while in one atrophy of three years' duration (case 12) was succeeded by superficial changes. In two others atrophy was always found without other types of inflammation. In Case 11 histologic confirmation of the gastroscopic diagnosis of severe atrophy was obtained. The postoperative development of a normal mucosa indicates a regenerative ability sufficient at least to provide a gastroscopically normal surface.

Gill (21), in gastroscopic observations of the response to insulin and histamine in atrophic gastritis, noted a diminution of secretory function which suggested the presence of a degenerative process. Schindler and Serby (24) on the basis of their experience with 22 patients with pernicious anemia concluded that liver therapy failed to produce consistent changes in the mucosa as seen gastroscopically. An increase in severity or regression or absence of change occurred in an unpredictable manner. Jones, Benedict and Hampton (25) in observing five patients with pernicious anemia found atrophy during relapses and an apparently normal mucosa in the period of remission after treatment. The question arises as to whether this is simply regeneration, disappearance of atrophy, or healing of an inflammatory process. The studies of Faber and others indicate that definite inflammatory changes are present in severe atrophic gastritis. While the gastroscopic findings in atrophy can be correlated roughly with the histologic appearance no definite inferences can be made as to the course the inflammatory process will follow. In general our observations indicate that severe and widespread atrophy tends to continue unchanged, but, as Case 11 illustrates, this is not always true. Furthermore the return of the mucosa to a gastroscopically normal appearance does not prove the presence of a normal mucosa for, as in pernicious anemia during a therapeutic remission, the apparently normal mucosa is unable to secrete acid gastric juice. The incidence of atrophic gastritis at gastroscopy in various series averages slightly

more than 10 per cent. Atrophy of the gastric mucosa seems to occur in gastric carcinoma, anemia and achlorhydria with a frequency greater than one would expect on a purely accidental basis but the relationship of these various processes remains unclear.

Carey (9) reported 20 polyps in 132 patients with atrophic gastritis. Jenner (9) found an incidence of carcinoma of the stomach of 4.42 per cent in 181 patients with pernicious anemia. Rigler et al. (26) recorded that in 293 cases of pernicious anemia over 45 years of age in 43,021 consecutive autopsies, there were 36 carcinomas of the stomach, an incidence of 12.3 per cent, three times the incidence observed in non-pernicious anemia patients of the same age group. In a roentgenologic study of 211 patients with pernicious anemia 17 (8 per cent) were found to have carcinoma of the stomach and 15 (7.1 per cent) benign gastric tumor, a total of 32 or 15.1 per cent. These observations constitute further evidence of an etiologic rather than an accidental relationship between pernicious anemia and tumors of the stomach.

Irradiation Therapy and Gastritis

In six patients with benign gastric ulcer and various degrees of hypertrophic, superficial and atrophic gastritis, radiation (x-ray) therapy was administered to the gastric fundus as a means of reducing gastric secretion. The gastroscopic pictures observed subsequently are of interest.

Case 3 with mild hypertrophic changes during the first two years of observation developed severe superficial gastritis after x-ray therapy. This continued in the next two years and was followed by a hypertrophic phase during the subsequent two years. Mild superficial gastritis was repeatedly found during the following four years.

Case 4. Superficial changes were noted in six examinations over a 14 month interval prior to radiation therapy. In six months after therapy two gastroscopic examinations disclosed the same picture.

Case 5. The single gastroscopy prior to radiation disclosed an essentially normal picture. In the two subsequent years hypertrophic succeeded by superficial changes followed by a normal mucosa with a return to a moderate hypertrophic appearance were observed.

Case 6. A single gastroscopy four months before radiation disclosed slight hypertrophic gastritis of the midportion of the stomach. Moderate to severe superficial gastritis was present in the lower stomach in the three years following x-ray therapy. The upper part of the stomach was normal until the fourth year when atrophic features were noted and persisted during the next five years.

Case 12. In two examinations prior to radiation the mucosa appeared essentially normal. In the subsequent six months slight atrophy was first noted

followed by the appearance of a normal mucosa. In the following year the atrophy recurred and persisted, but was only mild in degree.

Case 14. Hypertrophic gastritis, present for two years, was replaced by atrophy during the four years following x-ray therapy. A second course of roentgen therapy at this time produced no detectable change in the atrophic mucosa, after 25 days.

In these six patients x-ray therapy was followed by atrophic changes in three while in three others superficial and hypertrophic variants were noted. Theoretical considerations might suggest the appearance of an atrophic gastritis following radiation, but the almost invariable return in time of a normal secretory response argues against this concept (27). In this small series the changes observed were neither marked nor consistent.

Vagotomy and Gastritis

While the influence on the gross appearance of the gastric mucosa of factors, mediated through or by the vagus, is not known, certain observations following vagotomy are worthy of comment.

Case 4. Superficial gastritis was present for two years followed by severe hemorrhagic hypertrophic changes on the examination just before vagotomy. Slight diffuse superficial changes were present 14 days later.

Case 5. Various degrees of hypertrophic and slight superficial gastritis alternated with a normal mucosa in an unrelated sequence during two years, as observed on fourteen examinations. Following vagotomy similar superficial changes varying in degree from slight to severe were present in six examinations in two years. No hypertrophic changes were noted.

CONCLUSIONS

1. Chronic gastritis as diagnosed gastroscopically tends toward a persistent or recurrent course with most unpredictable variations in type, severity and location in the stomach.

2. Repeated examinations of two patients with quite consistently normal findings suggest the tendency of the normal stomach to remain normal. On the other hand, phases of normality were not infrequently found in stomachs usually exhibiting a chronic gastritis of one kind or another.

3. Repeated examinations in individual patients over periods varying from 2 to 11 years suggest that superficial and hypertrophic gastritis may be variations of the same process rather than separate and distinct entities. The prognostic implications of both the moderate and severe grades of superficial and hypertrophic gastritis are not significantly different, both tending to prolonged chronicity.

4. Atrophic changes without an admixture of the superficial or hypertrophic types were observed to be constant for periods up to five years; on the other hand, in some cases atrophic gastritis did seem to appear as a sequela of hypertrophic and superficial gastritis.

5. Atrophic gastritis, when severe, tends to persist, but return to normal has been observed.

6. Atrophic changes are more frequent in the upper third of the stomach whereas superficial and hypertrophic changes occur more often in the middle portion.

7. Gastritis of various types has been observed gastroscopically in many examinations in 14 patients over periods up to 11 years in duration without detectable serious consequence.

8. In these 14 patients it has not been possible to correlate the appearance of the gastric mucosa with symptoms of any kind.

9. While mucosal changes were observed in six patients subjected to x-ray therapy the type of change was not constant or consistent and could not be correlated with the appearance of the mucosa prior to roentgen irradiation or with the therapy itself.

10. Two patients with both superficial and hypertrophic gastritis prior to supra-diaphragmatic bilateral vagotomy were found to have only superficial changes after the operation.

11. Regardless of attractive theoretical considerations the clinical significance of chronic gastritis remains unproved.

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RESULTS OF HIGH CALORIC FEEDING

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INTRODUCTION

Many patients with acute surgical and medical conditions die because they are not fed. This fact is emphasized in the following resume:

In August, 1944, there was admitted to this hospital a semi-comatose, stuporous soldier. One month previously, he had been severely wounded in the right leg. Immediate operation had to be postponed several days while the effects of severe hemorrhage and profound shock were being overcome. A low thigh amputation was then carried out. On admission, severe sepsis, anemia and generalized edema were present. Re-amputation at a higher site for a bacillus *Welchii* infection controlled the sepsis but failed to alter a rapidly declining course, so that the outlook for recovery appeared doubtful. This clinical picture, coupled with an elevation of the serum non-protein nitrogen to 180 mgm. per cent and of the creatinine to 5.0 mgm. per cent, led us to suspect the existence of a so-called "hepato-renal" syndrome. This disintegration of his nutritional state was so impressive that it was decided to attempt to treat this grave defect. We undertook an intensive feeding program and withheld all other therapy. Four weeks later, the patient was well.

The lesson learned from feeding this patient led to the inauguration of a controlled program for the management of the malnutrition so commonly observed in the patients entering this hospital. The effects of the giving of large quantities of food to 78 soldier-patients is the basis for this report.

The indication for feeding a high caloric diet to these cases was determined more or less by the recognition that malnutrition was the paramount consideration. Accordingly, we treated a heterogeneous group of patients afflicted with acute infectious hepatitis, serious abdominal injuries, chest wounds, malaria, gastrointestinal diseases and neuropsychiatric states.

THE REGIMEN AND RELATED PROBLEMS

The program developed entails a daily consumption by each patient of food yielding a minimum of 5000 calories per day. A schedule of hourly feedings is employed starting with a full breakfast at 0800 and concluding at 2100 hours (table 1). The supplementary hourly feedings do not exclude, but rather supplement the three regular meals.

To avoid monotony, our menus are as varied as the situation of an overseas hospital permits. In general, the average food intake exceeds 5000 calories

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for each 24 hour period and provides 600-800 grams of carbohydrate, 150-250 grams of protein and 150-250 grams of fat.

TABLE 1
Typical daily menu schedule

				P	C	F	CALORIES
0800	Breakfast	Fruit Juice	150 cc.	0.6	16.6	0.1	70.0
		Milk	100 cc.	3.5	4.9	3.9	69.0
		Bran Flakes	30 gm.	3.0	21.4	0.6	103.0
		Sugar	25 gm.		25.0		100.0
		Eggs, scrambled	2	12.8	0.8	11.6	159.0
		Bacon, 2 slices	15 gm.	3.0	0.2	9.8	101.0
		Coffee, milk and sugar	25 gm.	2.2	28.0	2.4	142.0
		Bread and butter	40 gm.	3.2	20.8	9.3	180.0
0900	Dinner	Sandwich, bread, butter, jam and peanut butter		10.4	69.0	17.3	473.0
1000		Malted milk and cake		10.3	50.3	17.4	399.0
1100		Pineapple, sliced		0.8	42.2	0.2	174.0
1200		Ham	90 gm.	18.3		20.1	254.0
		Potatoes	100 gm.	2.0	19.1	0.1	85.0
		Peas	100 gm.	3.3	10.1	0.2	55.0
		Pear, canned	75 gm.	0.3	27.6	0.1	112.0
		Bread and butter	40 gm.	3.2	20.8	9.3	180.0
	Supper	Coffee, milk and sugar	25 gm.	2.2	28.0	2.4	142.0
1300		Malted Milk	100 cc.	9.8	18.0	9.1	193.0
1400		Sandwich, bread, butter and corned beef		22.6	41.6	17.2	413.0
1500		Eggs, hardboiled	2	12.8	0.8	11.6	159.0
1600		Sandwich, bread, butter and chicken		21.2	41.6	15.9	394.0
1700		Meat loaf	85 gm.	19.7		6.5	137.0
		Lima beans	100 gm.	7.5	23.5	0.8	131.0
		Asparagus	50 gm.	0.9	1.5		10.0
		Bread and butter	40 gm.	3.2	20.8	9.3	180.0
		Cake	75 gm.	3.5	32.3	8.3	218.0
		Cocoa	400 cc.	13.2	38.6	17.1	361.0
1800		Peaches, canned	100 gm.	0.4	18.2	0.1	75.0
1900		Sandwich, bread, butter and jelly		6.4	55.8	10.1	350.0
2000		Eggnog	100 cc.	9.8	18.0	9.1	193.0
2100		Malted Milk	100 cc.	9.8	18.0	9.1	193.0
Totals...				213.9	713.5	229.1	5805.0

Ca	P	Fe	VIT. A	THIAMIN	RIBOFLAVIN	NIACIN	ASCORBIC	VIT. D
gm.	gm.	gm.	IU	mcg.	mcg.	mg.	mg.	IU
2.3	4.3	42	10613	4409	7856	38	114	278

Two types of diet are utilized: (1) a high carbohydrate, high protein, moderately curtailed fat diet solely for patients with hepatitis, and (2) a regular diet.

The Army diet is well balanced. Hence, the addition of vitamins has not been considered necessary. Supplementary feedings may be of unlimited variety, but in this hospital, the available items are more or less restricted by the available supply to the following items: Bread, butter, cheese, peanut butter, jam, meats, eggs, tuna fish, salmon, chicken, malted milk and other milk beverages, puddings and cake (table 1).

The employment of a full dietary for acutely, often seriously, ill patients veers sharply from the orthodox patterns of convalescent feeding. The rationale of a full diet, however, has much to commend it. Liquids occupy a volume in the stomach out of proportion to their caloric producing potential. Although fruit juices are a good source of vitamin C and carbohydrate, they do not forestall protein deprivation or electrolyte deficiency. On the other hand, whole milk is an excellent source of protein, vitamins, minerals, and a fair source of energy though its water content is disproportionately high. Powdered milk¹ with the addition of sugar, eggs and vanilla largely eliminates this objection and has proved to be a valuable adjunct to the hourly feeding program.

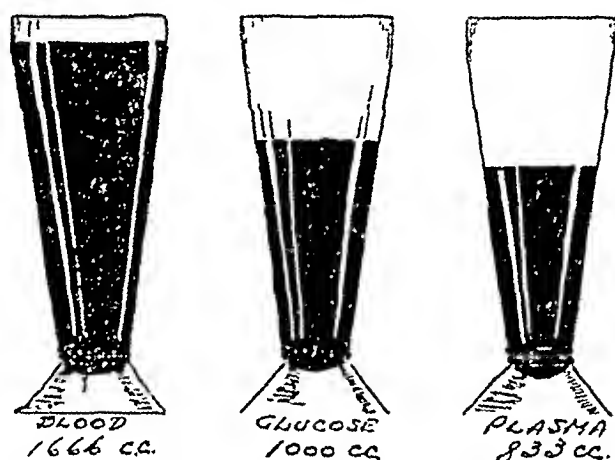
The administration of food by the oral route, as practised in this series of patients, is the preferred method inasmuch as normal physiologic processes are brought into operation. Only in this way can sufficient intake be maintained indefinitely. It follows that the patient's general nutrition will improve in proportion to the amount of food, particularly protein, ingested. The better the nutrition of the patient, the more rapid will be the recovery rate.

Unfortunately, it is assumed by the medical profession that the food capacity of even normal persons is confined to narrow limits, not to mention the supposed limitations of inactive, ill individuals. The limits of total food consumption have not been clearly defined in the literature, though it is generally admitted that most adult patients will not ingest more than 100-150 grams of protein in a day. Reported instances of forced alimentation are not frequent. Cuthbertson (1) cites two references in burned patients. One case treated by Taylor, Levenson, Davidson, Browder and Lund was fed by both vein and stomach tube. He received "some 500 gm. of protein daily and the enforced feeding was maintained for more than 42 days and the patient is stated to have made a remarkable recovery." In the second case, "Co Tui and his colleagues have shown that, in the later stages, burned patients fed a diet high in calories and high in amino acids . . . could be kept in nitrogen balance." Cuthbertson adds: "The administration of amino-acids in amounts equivalent to 66 gm. of nitrogen and calories to the extent of 6,550 is surely almost exceeding the physical capacity of the patient." Yet, it will be shown in this paper that a calorific

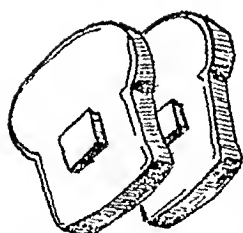
¹ The formula employed in this dietary is as follows: Powdered milk—ten pounds; Egg powder—two and one-half pounds; Sugar—three pounds; Vanilla—to taste; Water—to make five gallons. Contents per 100 cc.—Protein 8.8; Fat 8.7; Carbohydrate 16.0; Calories 187.5. This preparation may be flavored with malted milk, cocoa, maple or flavored syrups.

intake well beyond 6000 and a protein consumption between 150–250 grams is digested, absorbed and utilized.

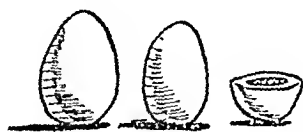
The custom of using blood, plasma, serum and glucose for their intrinsic caloric value is many times unjustified and unnecessary. Plasma is primarily indicated to correct acute and critical protein deficiencies from an osmotic



Equals



bread + butter, 2 Sl: $3\frac{1}{4} \times 3\frac{1}{4} \times \frac{1}{4}$ — ham 1 Sl: $4 \times 4 \times \frac{1}{8}$ — $1\frac{1}{4}$ Medium Potatoes



2½ eggs



100 cc. melted milk

FIG. 1. EACH FIGURE REPRESENTS 200 CALORIES

standpoint, but its value as a source of available protein for the body tissues is limited and impractical (fig. 1). The administration of sufficient plasma or whole blood to provide 150 gm. of protein would require approximately 2000 cc. of plasma or 4000 cc. of whole blood. Many donors would be necessary to supply this volume of blood. Elman also emphasizes that the parenteral route

for feeding should be merely an accessory one to the oral method and not a substitute (2). Cuthbertson says, "It is obvious that there is no point in giving protein hydrolysates to patients who can ingest, digest and absorb sufficient protein to serve their requirements" (1).

The urgency for intravenous feeding is most critical in the period immediately following major operations. Elman has developed the intravenous use of amino acids (2). The administrations of hydrolyzed casein mixed in a solution with glucose (Elman) provides 80 grams of protein and a total of 1600 calories in a 24-hour period, whereas the feeding of two ham sandwiches and two glasses (600 cc.) of eggnog provides 96 grams of protein, yielding 1884 calories (table 1).

We took cognizance of the problem of narrowing the gap between the seemingly insurmountable resistance to consuming such a quantity of food and the sick patient's theoretical metabolic requirements. It is an often overlooked fact that food offered a patient is of no value unless it is eaten. Reliance upon the statements of the patient that he has eaten his food has been found misleading. An inspection of trays and garbage cans in Army hospitals lends ample proof of this observation. Further, a careful survey of the average diet in two Army hospitals in North African Theatre of Operations (3) recently disclosed that patients with hepatitis rarely finished the tray of food and often consumed as little as 800 calories in a day. Nevertheless, *physicians are wont to take it for granted that their patients are consuming the food which they have prescribed, and are lulled into a false sense of security.*

To assure the ingestion of a high caloric dietary postulated in theory, a ward staff consisting of one nurse and two non-commissioned officers were selected. Under the supervision of one of us (JIG), in liaison with the dietitians, each member of this staff was taught that phase of dietetics which applied to these patients on the feeding regime. Their duties were so arranged that each one could substitute for another when necessary. The patients on the hourly feeding regime are the sole responsibility of this staff, and they have found it practicable to care for as many as 30 patients at a time. Each day, the three regular meals are prepared in the hospital kitchen and brought to the ward in food carts at mealtime. The supplementary feedings are prepared in the ward kitchen. One member of the dietary staff is present during each feeding hour to oversee the actual consumption of food, and a diary is kept of the exact amount of food consumed by each individual at each feeding. By this method, the recalcitrant patient can be noted promptly and given additional attention. The total quantity of food consumed in a day is broken down into the actual carbohydrate, protein and fat content from which in turn the total caloric yield is computed. These figures are readily available on a daily record prepared for this purpose (table 2). An important aspect of this regimen is the daily weight. The patients are weighed at 0900 hours at the bedside and a graphic

record is kept. In our experience, there has been no contraindication to weighing any patient except in the early postoperative days.

On the surface, the justification for the rather large volume of clerical work may be questioned. In addition to its academic value, there seems to be practical justification for such a practice. The physician in charge can detect at a

TABLE 2

Case #5

(Name)		(Rank)		(ASN)	
Malaria					
(Diagnosis)					
165		152		152	
Maximum Weight)		(Minimum Weight)		(Weight Now)	
DATE	WEIGHT	CALORIES	P	C	F
1 Nov.	152	4844.6	141.1	729.6	151.2
2 Nov.	152	4220.6	188.1	649.5	207.8
3 Nov.	154	4935.3	165.5	670.7	175.5
4 Nov.	156	4849.9	172.5	619.8	207.3
Malaria attack					
5 Nov.	155	4963.7	163.8	648.3	189.7
6 Nov.	154	4009.4	159.2	552.9	128.0
7 Nov.	152	4367.0	184.5	537.6	165.5
8 Nov.	152	3808.0	124.0	459.0	164.0
9 Nov.	156	4694.7	147.8	652.5	156.5
10 Nov.	156	4732.6	145.6	624.0	183.8
11 Nov.	154	4987.2	177.1	635.0	193.2
12 Nov.	154	5139.9	169.7	678.1	194.3
13 Nov.	154	5071.3	171.7	656.6	159.9
14 Nov.	159	4184.9	140.5	538.3	163.3
15 Nov.	158	4834.2	165.8	630.5	185.0
16 Nov.	159	4909.5	159.2	617.5	200.3
17 Nov.	156	5561.4	208.3	717.2	206.5
18 Nov.	154	4469.5	137.2	618.6	160.7
19 Nov.	156	3927.1	139.9	539.7	134.3
20 Nov.	156	4971.3	155.0	609.0	201.3
21 Nov.	159	4056.8	141.3	533.6	150.8
22 Nov.	161	5513.2	186.5	729.2	205.6

glance the patient who has not complied with the program and remedy the deficient intake. The patient looks favorably upon such careful supervision of his caloric intake and daily weight variation, and develops an enthusiasm for the therapeutic regime.

Anorexia. Failure of appetite is the foremost impediment to maintaining nutritional parity during illness. Authors doubt that it is possible to overcome

this seemingly inevitable component of febrile illnesses, injuries and serious operations. Thus, Lichtwitz, in promulgating the high food requirements which are necessary to maintain nitrogen balance during fever laments: "However, this necessitates a quantity of food that can scarcely be administered" (4).

Nausea is the well known sequel to persistent anorexia. The patient who develops nausea exacts a toll on the patience and fortitude of those thankless individuals who have the effrontery to impose upon him a full tray of food. This is a situation in which our staff and ourselves have been compelled to pit all our ingenuity against the inherent lack of desire of sick people to eat. Open hostility is frequently encountered.

The exact mechanism for the production of anorexia in febrile conditions is not clearly understood. There are more likely explanations for the anorexia which follows serious injury and/or operation, such as exhaustion, physical weakness or painful motions. In some cases, it is erroneously considered by the surgeon or nurse that the ingestion of food will prove deleterious. It is agreed that a starvation period several days in duration will cause the appetite to disappear. *In the end, starvation and anorexia produce a vicious circle.*

Adequate consumption of food from the very beginning prevents the development of anorexia, nausea and malnutrition. From the outset, it is carefully pointed out to the patient that the food intake must be considered in the nature of medical treatment for his illness; that appetite is most often a dependable guide except during illness; that during such an occurrence, when the body's needs are so greatly accelerated, one's best friend, his appetite, betrays him. In most cases, a logical explanation of the importance of food for recovery will suffice to initiate eating. It is possible to forecast complete relief from gastrointestinal discomfort after a period of 48 hours on the regime. The patient undertaking the feeding regime finds his greatest encouragement in his fellow patients who have already completed the difficult early hours of adjustment. The challenge, "If he can do it, I can," rarely fails. There is a constant interchange of conversation on the beneficial effects of this diet. In recalcitrant patients, the exhortations of fellow patients carry more weight than the continued insistence of the ward personnel. In general, a period of 48 hours will efface the untoward gastrointestinal symptoms interfering with food consumption and the appetite returns.

Vomiting. It has been learned that vomiting need not follow the ingestion of food by patients who have developed anorexia and nausea. The instances of vomiting during the administration of the feeding program have been so uncommon that they can be considered negligible. When present, recurrent vomiting proved to be a formed habit reverting back to childhood rather than an associated symptom of the illness. Such an individual would vomit after he had tolerated the hourly feedings for several days and his illness had improved.

The vomiting, apparently psychogenic in character, has not proved to be a contraindication to the pursuance of the program.

It has been found practicable, by means of the feeding plan outlined above, to deliver into the gastrointestinal tract of a sick patient a quantity of food which satisfies the most exacting metabolic requirements.

GENERAL RESULTS OF HOURLY FEEDING

In an Army hospital, the prime objective of treatment is the return of the soldier to duty with a minimal delay. Experience with the hourly feeding program leads us to believe that it contributed significantly to a reduction of the non-effective rate. An average weight gain in 78 patients of 14.5 pounds per patient eloquently depicts the type of response obtained. Rather than representing a mere weight gain, these pounds spared the further expenditure of the body tissues to meet the increased metabolic demands of disease. Also noteworthy is the ever-increasing sense of well-being that accompanies the gain in weight on the high caloric dietary.

Inasmuch as muscular wasting (atrophy) and emaciation result from prolonged inadequate protein intakes, abnormal fatigue, general lassitude and a disinclination for strenuous activities are more frequent manifestations of protein deficiency than edema. The possible rôle of nutritional deficiencies in connection with the fatigue syndrome may be overlooked clinically. The types of disorder encountered in our series of patients generally require a prolonged convalescence and a lengthy period of rehabilitation. Interesting to report is the absence of weakness and fatigability which has always been expected in patients getting out of bed after a long illness. The hepatitis cases, who average 30 days of complete bed rest, are customarily assigned to ward details on the first day out of bed. One week later, they are sent to rehabilitation wards to partake in the full program preparatory to duty. There has been no complaint on the patient's part of undue fatigue or inability to carry on such assignments.

These results indicate that the maintenance of nutritional balance throughout the entire convalescent period is a crucial factor accelerating the rate of recovery and return to duty. We believe it fair to say that many of the ravages of the illness can be thwarted by providing a sufficient quantity of food to maintain a positive weight balance.

HOURLY FEEDINGS IN SURGICAL CASES

In the face of unquestioned surgical management of the highest order accorded the wounded soldier, it is the rule to find that the importance of food intake has been overlooked. Weakness and weight loss arising in such cases is viewed by the surgeon as a necessary component of the clinical picture. The

prevalence of this type of occurrence has prompted the Committee on Convalescence and Rehabilitation of the National Research Council to emphasize the results of their survey as follows: "Reports from hospitals receiving the wounded from practically every theatre indicate the prevalence of malnutrition as shown by moderate to severe loss of weight. One published report records losses up to 30 kg. (66 pounds) in a series of patients with compound infected fractures evacuated from North Africa. . . . One observed case in a marine who sustained a gunshot wound through the left side of the chest in combat in the South Pacific illustrates the rapidity with which such loss of weight may occur. No surgical procedure was required. He had lost, when he was permitted to walk after three weeks, 37 pounds" (5).

Inasmuch as loss of body weight includes loss of protein tissue, the integrity of the vital processes concerned with wound healing and immunity to infection are inevitably threatened. Whipple (6) demonstrated that dogs stripped of their protein reserve have a lessened resistance to infection. The same author also showed that infections appear to have an inhibiting influence upon the body mechanism for producing plasma proteins. Continued fever and chronic suppuration bring about a progressive loss of tissue protein and anemia as well. Hypoproteinemia is often an underlying factor in the dehiscence of wounds (7) and can retard the healing time of undisrupted wounds.

Surgeons are accustomed to accept postoperative weakness as a normal sequel of operative procedure or injury. This may spring largely from the effects of malnutrition (protein deprivation) which have appeared surreptitiously. The recovery from such physiologic debility and the reestablishment of normal weight may well be a long, tedious process.

That extreme emaciation can follow an extensive surgical procedure is not doubted; however, the fact that inadequate nutrition during convalescence may in itself cause death from starvation per se is not fully appreciated inasmuch as wasting is not generally designated by the pathologist as the specific cause of death. To illustrate the course of development of extensive degrees of malnutrition, the following pertinent case is detailed:

Case report. A 26 year old sergeant was wounded in the abdomen by an exploding shell on 26 September 1944. There were two points of entry, one a deep penetration. First aid treatment on the field included the administration of penicillin, plasma, tetanus toxoid and morphine; a sulfonamide dressing was applied to the wound. ProFOUND shock delayed the exploratory operation until the following day. At operation, the peritoneal cavity was filled with blood and 3000 cc. were removed. The gall bladder and a piece of liver had been shot away and the former became bound to the hepatic flexure. The jejunum was the site of multiple perforations. It was sectioned in two places approximately two feet distal to the ligament of Treitz and an end-to-end anastomosis completed. The hepatic flexure was mobilized and a two-inch

portion of the colon removed with the gall bladder. A drain down to the gall bladder bed and another through the abdominal wall into the right lateral gutter was inserted. The two colostomy ends were exteriorized. Both sulfonamide and penicillin were inserted into the peritoneal cavity. He returned from this surgical operation with a systolic pressure of 80 mm.Hg. and a marked tachycardia. Postoperatively, he received large quantities of blood, plasma, glucose and one of the sulfonamides intravenously. On 27 September, a severe thrombophlebitis of the right arm appeared. On the fourth postoperative day, 1 October, he became icteric and by 14 October, this became extreme. The icteric index reached 307, the NPN 136 mgm. per cent and the total proteins measured 5.8 grams per cent. The prothrombin time was prolonged and the urine contained bilirubin, bile-stained casts and a small amount of albumin. The stool had become acholic. Despite the administration, in abundance, of blood, anemia was marked. The red blood cell count dropped to 2,840,000 and the hemoglobin to 9.48 grams on 16 October; there was a leucocytosis of 27,650 and the differential count showed 82% polymorphonuclear cells. On 22 October, his condition was described, "Not so good and weaker." Observers were struck by the extent of weight loss and debility. On 28 October, a copious drainage of bile came from the wound in the right flank. A decubitus ulcer developed in addition.

Upon admission to the surgical service of this hospital on 3 November, he appeared apprehensive and the skin had an ashen hue. A "very jaundiced, emaciated, weak and tired individual" was portrayed. The presence of extreme nausea interfered with food intake. Paregoric was administered to control the liquid fecal drainage. The surgical officer recognized the futility of specific treatment in an individual whose prime need was nutritional rehabilitation—whose very life hung in the balance. He was accordingly transferred to the medical service in order to attempt such feeding. Our examination at this time, 8 November, disclosed, in addition to the above findings, a small liver, leucocytosis of 29,000 cells, a bile fistula and a profuse liquid fecal drainage from the colostomy. There was a marked hypothermia, the temperature not exceeding 96°F. for several days. The high caloric hourly feeding regime with a moderate reduction in fat was prescribed. Bile salts were added. The decubitus ulcer was treated by a method described by one of us (JIG); viz., sulfathiazole powder applied topically and the use of a light cradle.

The patient vomited twice during the first 24 hours and once the next day. By 15 November (one week of feeding), marked improvement in vigor and his alertness was noted by everyone. In spite of occasional vomiting of small amounts of food, abdominal cramps, pyrosis, etc., the program of feeding was persisted in. Even at the outset, his intake averaged 3400 to 4632 calories during the first ten days. The stools, though clay colored, became more solid and voluminous. Within a month, the decubitus ulcer had healed completely. The bile drained profusely through the fistula. The urine contained bilirubin, granular casts, many white and red cells and a trace of albumin. It became possible to increase the food intake beyond 5000 calories per day with improvement in his general condition. On 22 November, after two weeks of planned feeding, it was possible to weigh him for the first time—the figure being 89 pounds. During these early stages of convalescence, there were mental aberrations as food idiosyncrasies, irritability, obstinacy, a tendency to self-pity and

even hostility. Coincident with moving the patient from a private room to the ward on 24 November, his attitude improved to such an extent that he consumed 7800 calories that day.

After one month of treatment, he got up in a wheel chair and took a few steps without assistance. Without urging, he consumed in excess of 5000 calories each day. There was a persistent leucocytosis, 15,000–20,000 cells per cu.mm. and a polymorphonucleosis above 80%. The red count reached normal limits, 4,470,000 and the hemoglobin 13.6 grams on 12 December.

A weight of 94 pounds was attained on 9 December. This modest gain of weight was belied by a disproportionate gain in strength and vigor. He walked normally and the general appearance was that of a normal, thin, individual rather than one of an emaciated, cachectic patient. At this point the weight level began to regress somewhat reaching a minimal figure of 91 pounds.

The injection of a radiopaque substance into the biliary fistula tract revealed that a portion of the hepatic duct still remained. At operation (Lt. Col. Lindon Seed), the proximal portion of the hepatic duct was anastomosed to the duodenum. The soldier returned from surgery in excellent condition having received 500 cc. of whole blood and 500 cc. of 5 per cent glucose during the operation. In the first 24-hour period, 1000 cc. of plasma, 1000 cc. of 10% glucose in 0.9% sodium chloride solution and 2000 cc. of 5% glucose in distilled water were given, yielding the equivalent of 1072 calories. On the second and third postoperative days, he consumed clear liquids which totaled 1292 calories in energy content. Penicillin and Vitamin K, parenterally, were administered for the first week following operation. The postoperative course was uneventful. The stool remained acholic and large amounts of bile continued to drain through the incision and fistula. At this stage, the patient became uncooperative to the extent that, despite vigorous efforts of everyone, his daily diet sheet revealed an intake varying between 1700–3600 calories in the period up to 10 January. On this date, the anastomosis began to function as indicated by the appearance of brown stools and a diminution of the bile flow from the fistula. Here there ensued a striking alteration in the mental state. Feedings were taken without complaint as indicated by a rise in the consumption of food beyond 5000 calories daily. One day, he consumed 6689 calories. Accordingly, the weight of 93 pounds recorded three weeks after the operation exceeded by two pounds the weight prior to surgery. He walked unaided and attended to all his needs. During the period of 19 January to 13 February, he gained a total of 30 pounds despite two operations for the insertion of clamps onto the spur of the colostomy. A peak weight of 135 pounds, representing a gain of 42 pounds in the preceeding 50 days, was reached on 10 March. On 12 March, the colostomy was closed and from this operation, there was also an uneventful recovery. The patient was returned to the United States.

Comment. In this striking case are embodied many of the lessons which the science of nutrition may contribute to the treatment of surgical patients. Here is a seriously wounded soldier, nearly exsanguinated, whose life was preserved by only the promptest treatment of shock and an heroic operation. Chemotherapy and parenteral administrations were utilized to their maximum

advantage. The development of severe hepatic damage (icteric index 307, NPN 133 mgm. %) and renal involvement (biluria, albuminuria, casts, red cells and white cells) during the early stages of convalescence suggests the presence of obstructive jaundice. The burden superimposed upon the body metabolism by a bile fistula, anemia, sepsis, thrombophlebitis and a decubitus ulcer are self explanatory.

For a period of over five weeks, this patient derived his exogenous caloric intake chiefly by the parenteral route. The lavish employment of blood, plasma and glucose undoubtedly equilibrated the electrolyte disturbances. The calculations of their energy content, however, indicate that from 26 September to 15 October, he derived from this source the equivalent of 291 calories per day. After this date, he took fluids orally according to his own desires. The inadequacy of such a course is amply attested to by a weight loss of 50 pounds in the 38 days prior to the institution of the high caloric feeding program. At this time the findings characteristic of a moribound individual were present—cachexia, extreme muscle wasting, an ashen hue and a hypothermia.

The nutritional deficiency was so acute that it demanded priority over all other more specific therapy. At first, it appeared doubtful that he could be persuaded to eat after such an extended period of starvation and serious illness. Whether the gastrointestinal tract, impaired by functional disuse for many weeks with an added handicap of a bile fistula and a colostomy, could utilize sufficient food to alter the course of the illness remained to be seen. Added to this bleak picture was a state of mental depression of a depth and persistence not often observed. The energies of everyone—dietitians, nurses, ward men and even patients—were enlisted to encourage his eating. How successful these efforts were can be seen more clearly in caloric figures in excess of 4000 calories for each of the first two days. Severe abdominal distress, cramps and vomiting were inevitable and had to be more or less ignored. Within a week, increased vigor and alertness were evident. The untoward gastrointestinal symptoms subsided. The probable weight on admission to this hospital can be estimated from the first weight figure of 89 pounds after he had consumed in excess of 4000 calories daily for a period of two weeks. During the following period of three weeks, there was a gain of six pounds which, subsequently, was partially nullified by a gradual decline of three to four pounds. It was our belief that there was not to be any further significant weight gain in the presence of a bile fistula. This prediction was borne out, after the bile fistula had been repaired by a gain of 42 pounds in a period of 50 days. Out of all proportion to the modest weight gain during the period of the bile fistula was a striking return of muscle power which enabled the patient to walk easily and do the necessary things for himself. Another significant attainment was a state of

body resistance which enabled him to withstand an extensive surgical procedure without any untoward complication.

In a very few days after institution of the high caloric regime, the liquid character of the fecal drainage disappeared. The most likely explanation hinges on the fact that protein deprivation had interfered with the normal physiologic dehydrating function of the colon. The healing of the decubitus ulcer in one month is in keeping with the recognized dependence of healing ulcers on a positive nitrogen balance. The return to normal of the blood picture in a similar period has also been shown to be related to adequate protein intake.

A patient came under our care who had sustained an avulsion type of wound of the abdomen in which most of the skin of the right lower quadrant of the abdomen, a goodly portion of the musculature of the belly wall in that region and a part of the cecum had been shot away. The remnants of the ileo-cecal gut had been exteriorized. Following his injury there had been a loss of weight of 50 pounds in 37 days. Here again, the patient had been fed exclusively for 12 days via the parenteral route with blood, plasma and glucose. After that period, he was offered food by mouth which, in large part, he had refused. The absence of complete records precluded an estimate of the caloric value of this diet. A large irregular stoma emptied the contents of the ileum upon a granulating wound approximately six inches in diameter and caused considerable excoriation of the skin over a much larger area. Closure of the cecostomy under these conditions was considered practically impossible by the surgeon, and he was referred to the medical service for forced feedings. On the controlled feeding program, he averaged over 5000 calories a day, including more than 200 grams of protein, for 23 days. In spite of the relatively enormous food intake, the fecal excretion became semi-solid and noticeably less irritating to the surrounding skin. In a month he had gained 20 pounds; epithelialization and cicatrization had progressed to a degree permitting closure of the cecostomy without incident.

Four patients with hemothorax were accepted for controlled feeding because of failure to regain weight, strength and to overcome anemia after the original condition had been alleviated. Two of these patients had failed to respond to adequate iron therapy for hypochromic anemia after the occurrence of the original injury. These men were still 18 to 26 pounds underweight. On a planned food intake during an average hospitalization period of 37 days, the mean caloric value of their dietary was 5343 including 172 grams of protein. The average weight gain was 15 pounds. The response of the two anemic patients was immediate and serves to reemphasize the important rôle of protein in hemoglobin synthesis (8).

Many soldiers recovered from wounds received in action fail to return to

duty because of weakness and inability to keep up with the rehabilitation program. Several of this type were referred to us. Analysis of the case histories revealed weight losses from 20 to 30 pounds. Frequently, there was an associated history of inadequate food intake during convalescence. After a period of controlled feeding averaging 14 days in three patients, there was an average weight gain of 10 pounds. The caloric intake averaged 5283 with 176 grams of protein. All of these patients were returned to duty.

Thus, even in less severe injuries, it is seen that greater attention to the patient's nutriment together with the more specific measures will, as it has in the more serious type, prevent, to a large extent, some degree of the disability commonly exhibited during the rehabilitation period.

ACUTE INFECTIOUS HEPATITIS

In spite of the evidence that an abundance of carbohydrate and protein is the key to the treatment of hepatitis, there are indications that relatively little progress has been made toward the fulfillment of this important dictum. The crux of the problem is epitomized in a recent survey (9):

"A recent report from *Natoussa* on infectious hepatitis described some results of a study of nutrition in relation to this disease. Analysis of diet records in general and station hospitals revealed average caloric values of the menus of 1,681 and 2,103, respectively, with values as low some days as 1,400 calories. The return of rather large amounts of uneaten food resulted in actual consumption of as low as 800 calories per day in many instances. Similarly, a recent survey of Canadian Army hospitals has shown significant discrepancies between the calculated and the actual consumption, with the result that steps have been taken to correct the situation."

"As the *Natoussa* report states, one of the disturbing features of acute infectious hepatitis is the rapid loss of weight during the acute phase, and the continuous loss of weight and strength and of tone and quality of the muscle if the disease becomes chronic." To further illustrate this point, one only need cite the long periods of debility seen during the so-called "yellow fever vaccine epidemic." In the types of hepatitis observed in the European Theatre of Operations, a proportion of the patients have not been fit for duty within the allotted period of 120 days and are sent to the United States for further recuperation. The mortality rate, though low, is not entirely insignificant. "There is evidence of other disturbances in nutrition as well. An^vadequate intake of food, especially protein, has clearly been shown to protect against severe liver damage in this disease and to hasten recovery and shorten the period of convalescence. Although the principal factor in this mechanism, appears to be protein (amino acid), the necessity for high caloric intake as a means of sparing protein and providing additional energy to limit weight loss and to promote recovery is^vwell recognized" (9).

Some of the factors contributing to the above untoward states may be gleaned from our histories. Many soldiers in combat come to dislike the vari-

ous field rations and eventually subsist on that small portion of it which they like. Some soldiers eat but one meal per day for weeks. Others are merely finicky eaters who limit their food intake to biscuits and/or cheese, candy and coffee. One of our patients, just as his father, had never eaten meat. In view of these observations, it seems that soldiers may become nutritionally below par even prior to the onset of hepatitis.

The early subjective symptoms of acute hepatitis—anorexia, nausea, post-prandial distress, vomiting, upper abdominal pain—are predominately gastrointestinal. These certainly are not conducive to eating. Consequently, it is customary to find upon admission that these patients are already below their normal weight. Twenty-five pounds is not an infrequently noted deficit.

Once the diagnosis of acute infectious hepatitis has been verified, the therapeutic dietary regime outlined by us is inaugurated promptly. The diet administered has an energy value of 5000 calories, derived from 150–250 grams of protein, 600–800 grams of carbohydrate and 150–200 grams of fat. To accomplish this goal, a schedule described in detail above (under “The Regimen and Related Problems”) has been arranged. This consists of three routine meals supplemented by hourly feedings extending from 0800 hours through 2100 hours. The fat content of this dietary is higher than that ordinarily employed. This appears to be justifiable in view of a menu of total energy content in excess of 5000 calories and a carbohydrate intake of 600–800 grams. It is of paramount importance that the patient consume each hourly feeding *in toto*. Though the symptoms of acute hepatitis are an obstacle to eating, they have not proved an insurmountable one. It is our experience to find that the apathy to food wanes and all the above mentioned discomforts subside within 48 hours. Invariably, there is noted an almost electric response in the patient’s physical and mental appearance. These patients did not receive any other form of therapy as the supplementary use of vitamins, amino acids or parenterally administered glucose and plasma. In our series of 18 cases, there was recorded an average gain in weight of 20 pounds per patient over a mean hospitalization period of 39 days. The graphic weight curve of Case 11 (table 3) illustrates the average response in acute infectious hepatitis. One of the severe cases (Case 2, table 3) gained 27 pounds during the first month of illness and in all a total of 46 pounds during 10 weeks of hospitalization. The icterus index reached a peak of 105, but he was ready for duty in 80 days. As a rule, the patients are kept in bed until the icterus index has dropped under 15. At this time they become impatient with bed confinement, and, when permitted to become ambulatory, are surprisingly strong and do not experience fatigue after mild exertion on the ward. This important result was unexpected in a disease following which patients have been wont to feel notoriously debilitated for protracted periods. It is the rule to find the soldiers in better condition

at the time of discharge (by their own statement) than prior to the onset of the illness.

Those patients in whom a marked degree of undernutrition had developed prior to admission to our hospital exhibited greater weight gains than those who arrived in a comparatively normal state of nutrition. Even during the acute stages of the illness, however, no patient lost weight.

In retrospect, it is admitted that the only objective of our treatment was dictated by the determination to apply in practice the principles of nutrition

TABLE 3

Hepatitis

CASE NO.	HOSP. DAYS	ADMIS- SION WT.	NORMAL WT.	DIS- CHARGE WT.	GAIN	AVERAGE DAILY INTAKE				GRADE INVOLVEMENT	PEAK ICTERUS
						Cal.	Prot.	Carbo.	Fat		
1	21	132		142	10	4061	132	674	93	Moderate	33
2	80	154	175	200	46	5285	160	844	141	Severe	105
3	53	134	140	158	24	5226	164	812	146	Moderate	20
4	52	166	180	188	22	4937	165	761	137	Mild	20
5	11	140		152	12	5206	162	802	150	Moderate	50
6	34	124		134	10	4586	150	740	114	Moderate	50
7	62	135	150	159	24	4547	151	736	111	Severe	85
8	35	180	185	186	6	4308	150	693	104	Moderate	30
9	20	124	135	136	12	4831	152	779	123	Mild	15
10	24	168	195	186	18	4890	169	734	142	Mild	21
11	26	148	165	172	24	5005	172	762	141	Mild	27
12	64	146	158	178	32	5087	166	766	151	Moderate	71
13	48	152	168	177	25	5189	163	772	161	Moderate	38
14	75	136	161	184	48	5150	168	782	150	Severe	140
15	45	144		159	15	5019	170	743	151	Moderate	57
16	19	147		161	14	5520	193	782	180	Moderate	45
17	23	148		164	16	5597	196	796	181	Moderate	30
18	14	172		178	6	5531	191	780	183	Moderate	80
Average....	39				20	4999	165	764	142		

promulgated in liver disease by modern authors. Little did we suspect that the direct benefits of such a high caloric diet as utilized here would include an increase in body weight during the most acute phases of the illness. Complete restoration of the soldier's physical and mental status on this dietary indicates that the high grade debility encountered in hepatitis is a direct offshoot of an inadequate intake of food during and sometimes prior to the illness.

Each of the patients in this series with acute infectious hepatitis upon recovery was capable of performing duty after one week in the rehabilitation wards.

HIGH CALORIC FEEDING IN MALARIA

The following excellent summary exemplifies present-day thinking regarding feeding febrile states (10): "The prevailing system at the present time may be fairly described as that of feeding a fever patient up to the limits of his digestive capacity with fluid or semi-fluid food, except, perhaps, in the case of some abdominal fevers

"Any lingering doubts as to the wisdom of the feeding plan tend to be dispelled by the results of researches which have shown, (1) that the free administration of food does not, as was formerly supposed, tend to raise the temperature of feverish patients; and (2) that the food is not merely poured into a digestive apparatus unable to deal with it, for the absorption of light articles of diet, at any rate, goes on as perfectly in the febrile state."

With the administration of a diet exceeding in values 5000 calories per day we have learned that the digestive capacity of febrile patients is greater than has been supposed. Furthermore, as emphasized above, it has proved wise to minimize the fluid and semi-fluid foods in favor of the more productive solid foods of a regular diet. In febrile patients, such food is absorbed equally well and makes possible larger caloric intakes than the more fluid diet.

"It has been shown (from the same excerpt) that a great increase of metabolism occurs during fever and Coleman and DuBois found in cases of typhoid fever that the basal heat formation rises and falls in a curve roughly parallel with the temperature, and at the height of the fever is 40-50 per cent above the normal. .

"If a healthy patient is starved the fat and protein of the body supply the bulk of the calories which are produced. Thus Benedict estimated the metabolism of a starving healthy man, and the average figure for the seven days showed that 1690 calories were burnt and these were supplied by 139.8 grammes of fat, 69.5 grammes of protein, and only 23.6 grammes of carbohydrate. The chief loss of weight is due to the consumption of fat, though the weakness of the muscles attracts especial attention to the destruction of protein. In fever the actual loss of muscle may be serious. In the seven days of the fast 486.5 grammes of protein were lost, which is equivalent to a loss of 1.88 kilogrammes in weight—

"The work of Shaffer and Coleman, and Coleman and DuBois, on the metabolism of typhoid fever, has shown that the average metabolism of a patient with typhoid fever is 40 calories per kilogramme, or 2400 for a man of 65 kilogrammes (10 stone 3 lb.). A healthy man was easily kept on a nitrogenous equilibrium on this number of calories, but the typhoid patient required 52-80 Calories per kilogramme (3600-5000). It is difficult to understand what happens to this great excess of calories. Coleman and DuBois showed that the protein, fat, and carbohydrate were perfectly digested and absorbed and that some fat might be deposited in the tissues, although protein loss was continued The great disturbance in metabolism is believed to be due to the action of toxin and not to the actual height of the temperature, since

Graham and Poulton showed that destruction of proteins did not occur when the temperature was raised for some hours

"We have taken typhoid as our type, but the same principles apply to other fevers, and the convalescence from these would be much shorter if more food were given. A patient with influenza often has little appetite and does not want to eat meat or fish, but eggs can be added to milk and 200-400 grammes of sugar can be added to lemon or orange drinks, and thus raise the caloric value considerably. Even in a short fever, at least 2000 calories should be given if possible and in a long one this should be increased to 3000."

Why this work has lost itself upon the profession, as applied to other fevers than typhoid, the incidence of which is very low, is understandable in the light of our experience. The physician is loath to incur the wrath and ill-will of his sick patient to whom the mere mention, smell and sight of food is repulsive during a relatively brief febrile illness such as influenza. The above quoted authors clearly recognize the importance of feeding the shorter febrile illnesses and recommend at least 2000 calories per day. As shown here quantities of solid food in excess of 5000 calories can be expeditiously administered in the acute stages of a febrile disease.

During the present conflict, malaria has proved to be an obstacle in keeping an effective fighting force in the field. It has been repeatedly demonstrated that recurrent malaria is not compatible with efficient combat duty. Following malaria there ensues a train of symptoms characterized chiefly by debility, loss of weight, strength, and most important a sheer inability to carry on the required work.

Analysis of the cases from a nutritional standpoint reveals a weight loss of 10 to 12 pounds during an acute episode of chills and fever, three to seven days in duration. In the interval between attacks, there is often in sufficient time to regain normalcy. In this manner, an extreme degree of undernutrition may supervene. There are several possible explanations for the rapid weight loss during malaria over and above the changes which occur during any febrile illness. The average 7.2% increase in the basal metabolic rate for each degree of Fahrenheit rise in temperature during fevers is not to be regarded as insignificant with respect to protein needs and losses (11). Whereas, during fever, oxidations in the body are notably increased, the production of heat may be augmented as much as 200 per cent during a chill. In malaria, it has been shown that the metabolism actually rises even before the onset of the chill (Lichtwitz (4), p. 31). Kopp has noted a marked drop in the serum proteins of patients with acute recurrent malaria (12).

As shown by the above observations, undernutrition is an important sequel of malaria. Weight losses of 20 pounds and upwards are commonplace. Such patients may feel subjectively well in a hospital ward only to become rapidly

exhausted by the rehabilitation program. In effect, even the symptoms generally designated "post-malarial," namely, headache, dizziness, anorexia, backache and nervousness are indistinguishable from those which follow malnutrition as will be evident below.

That the above effects are primarily nutritional in origin is readily demonstrated by our series of ten patients on high caloric feeding. These patients consumed a regular diet with a caloric value in excess of 5000 calories derived from 150-250 grams of protein, 600-800 grams of carbohydrate and 150-250 grams of fat. The hourly schedule outlined above (table 1) was adhered to. An average weight gain per patient of 12 pounds in 28 days was obtained. The benefits of feeding are not long delayed as shown by the disappearance of "post-malarial" symptoms in a matter of days. This seems to indicate, as in hepatitis, that the returning strength rather than weight gain alone, plays the decisive rôle in the waning of the vague complaints. Some patients stated that they hadn't felt so well since the onset of malaria months before. It must be acknowledged that we were tempted at the beginning to suspect that the vague complaints in such patients represented a tendency to exaggeration. This opinion had to be revised following a period of feeding. All the patients, literally disabled from Army service for a period of months previously, were able and anxious to return to duty.

Four of the ten patients experienced acute bouts of malaria while on the feeding program. This provided an opportunity to continue the high caloric intake during the febrile period. Though more difficult during the acute stages, feeding must not be relegated to the whims of the patient. After the attack had been brought under control by specific malarial therapy (13), the patients showed little or no weight loss.

The successful results observed on a high caloric intake during the acute febrile stages of malaria, wherein the temperature reaches levels of 104°-105°F., should point the way to further application of this principle. On the basis of feeding these malaria patients, other febrile states as pneumonia, the exanthemata, and meningitides should be amenable to similar treatment.

NEUROPSYCHIATRIC STATES

Nineteen patients with neuropsychiatric disorders received the high caloric feeding program. The cases were admitted directly with gastrointestinal diagnoses or referred from the psychiatric department for controlled feeding. All patients comprising this group had in common the findings of undernutrition. The psychiatric diagnoses of this group embraced the following: Psychoneurosis, chronic, severe (6); psychoneurosis, hysterical type, moderate (1); constitutional psychopathic state, inadequate personality, moderate (1);

psychoneurosis, anxiety state, acute, moderate—combat exhaustion (5); nervous vomiting, moderate (3); nervous diarrhea, moderate (3) (table 4).

These patients received a regular diet yielding 5000 calories per day, derived from 150–250 grams of protein, 600–800 grams of carbohydrate and 150–250 grams of fat on the schedule outlined in table 1. It was circumstance that the neuropsychiatric cases on this dietary were intermingled with other patients who were being given the same regime for organic disease.

The average weight gain of the entire group in 26 days was 11 pounds. In

TABLE 4
Neuropsychiatric

CASE NO.	HOSP. DAYS	ADMIS- SION WT.	NOR- MAL WT.	DISCHARGE WT.	GAIN	AVERAGE DAILY INTAKE				TYPE	GRADE INVOLVEMENT
						Cal.	Prot.	Carb.	Fats		
1	54	125		135	10	6347	182	957	199	Hypochondriasis	Severe
2	38	118	132	118	0	4424	150	596	160	Hypochondriasis	Severe
3	25	157		167	10	5622	182	778	198	Anxiety	Severe
4	29	145	170	146	1	5780	189	779	212	Hypochondriasis	Severe
5	23	137		145	8	5154	167	673	199	Hypochondriasis	Severe
6	18	123		130	7	5529	189	748	209	Hypochondriasis	Severe
7	36	162		178	16	5339	175	712	199	Hysteria	Severe
8	25	162	165	175	13	4983	170	682	175	CPS. inadequate	Moderate
9	32	152		169	17	5342	174	698	206	Combat exhaustion	Moderate
10	37	154		163	9	4713	161	628	173	Combat exhaustion	Moderate
11	19	176	196	186	10	4783	160	669	163	Combat exhaustion	Moderate
12	17	145	153	160	15	5135	162	719	179	Combat exhaustion	Severe
13	22	148	160	162	14	5455	184	723	203	Combat exhaustion	Severe
14	15	139		145	6	5181	174	696	189	Nervous vomiting	Moderate
15	13	175	190	186	11	5325	179	709	197	Nervous vomiting	Severe
16	26	136	150	156	20	5305	173	692	205	Nervous vomiting	Moderate
17	27	140		155	15	5199	184	695	187	Nervous diarrhea	Moderate
18	16	124		138	14	5478	183	750	194	Nervous diarrhea	Moderate
19	20	126	160	139	13	5800	203	761	216	Nervous diarrhea	Moderate
Average....	26				11	5315	176	719	193		

evaluating the results of patients consuming this dietary, there is a natural division; those with symptoms of longstanding and those of more recent duration.

In the former group, chronic psychoneurosis, there was initially a significant weight gain, alleviation of symptoms and a more vigorous appearance. It is significant that two of these patients gained as much as 10 pounds each in approximately 10 days. During the subsequent few weeks on the same caloric intake (5000 calories or above), the weight levels regressed toward the initial figure. Coincidentally, the presenting symptomatology reappeared and the newly acquired sense of well-being was lost.

In the latter group, including patients with nervous vomiting, nervous diarrhea and acute anxiety states of recent origin, there was a more tangible improvement. The average weight gain (13 pounds per 22 days of hospitalization) on an intake no greater than the former groups was more prompt and enduring. Thus, cases 14 and 19 with nervous diarrhea or nervous vomiting, maintained their weight gains (as much as 20 pounds in case 16), and were salvaged for further service in a non-combat capacity. A most gratifying response to high caloric feeding was obtained in three instances of combat exhaustion, cases 9 to 13 inclusive. These men all had a uniform history: Long strenuous periods of active combat, inadequate intake of field rations, significant loss of weight, and, finally, the development of a psychogenic symptomatology of the anxiety type. Aside from the weight gain, these patients exhibited rapid degrees of improvement in their subjective complaints, physical appearance, and best of all, in the state of the nervous system. Although one might be tempted on the basis of their general appearance to return the soldiers to combat duty, it was deemed advisable by the consulting psychiatrist to reassign them to non-combat duty. A similar group of cases was reported by Clarke and Prescott (14) dealing with 17 cases of vitamin B deficiency. The patients were primarily those with functional nervous disorders in whom were present symptoms of loss of appetite, lack of energy, fatigue on slight exertion, nervous dyspepsia and so on. It was emphasized by these authors that the deficiency was "actually precipitated only when the mental or physical factors led to loss of appetite or impaired absorption." Similarly to our cases striking improvement occurred as the result of vitamin therapy without special psychologic measures or alterations of the environment.

In the main, the clinical results in the above cases are commensurate with the rapid rate of restoration of weight, strength and sense of well-being. The regime is not advocated as a mode of therapy to be compared with established treatment of these types of patients. However, the high caloric feeding appears to have a definite place in patients who exhibit recent weight loss from a traceable cause, namely, an inadequate dietary during a period of prolonged nervous stress.

DISEASES OF THE GASTROINTESTINAL TRACT

Idiopathic ulcerative colitis. Three patients with idiopathic ulcerative colitis came under our observation. Reviewing the clinical histories of these patients, the following common features were noted: Their initial attack of prolonged, bloody diarrhea; recent onset of symptoms; four-to-twelve months of combat; and a 10-30 pound weight loss. Each patient had the proctoscopic and roentgen findings characteristic of the disease. Because the nutritional state of each patient appeared to warrant special consideration, the high caloric feeding

program was instituted. The patients were placed on the regular diet outlined under "The Regime and Related Problems" (table 1). To observe the effects of penicillin in this disease, each patient was given 20,000 units intramuscularly every four hours for seven days. There were weight gains ranging from nine-to-thirteen pounds on hospital stays of 13-29 days. Coincident with the weight gain was the all-important reappearance of well-being, strength and vitality common to patients on the feeding program. Within 48 hours after the introduction of combined dietary and chemotherapy, the stools were reduced in number from 8-10 liquid or more to 2-3 soft per day. At the time of discharge, the proctoscopic picture was normal in each instance and the roentgen findings significantly improved. The known chronicity of idiopathic ulcerative colitis precludes prognostications of the future course of the disease. Hence, these patients were returned to the United States.

Amebiasis. The effect of high caloric feeding in a soldier with amebiasis is of interest. He had recovered from a battle injury and was transferred to our care upon the identification of *entameba histolytica* in the stools. He had been hospitalized and treated for amebiasis on two previous occasions with the usual emetine and carbarsone medication. The response to treatment had been slow. In fact he had been hospitalized for 11 of the previous 14 months for this ailment. There were 20-30 bloody, watery stools for the preceeding several weeks. There was such a notable degree of malnutrition, and he was 27 pounds under his normal weight, that a full diet (table 1) was instituted together with the specific medication—emetine and carbarsone. Within 48 hours his bowel movements diminished to one normal stool per day for the first time in many months. He consumed a menu with a caloric value well in excess of 5000 calories daily containing 200 grams of protein, an equal amount of fat and 800 grams of carbohydrate. After 28 days of this dietary, he had gained 18 pounds. The stools remained normal in character and were clear of parasites. The return of normal physical strength and vitality was most notable. The achievement of a positive nitrogen balance in chronic diarrhea on a high caloric, high protein diet of moderate residue appears to be somewhat unique. Barger and others (15) claim that nitrogenous food material leaves the body at a more rapid rate than it can be absorbed in such conditions as ulcerative colitis, dysentery and the sprue syndrome. Edema of the gastrointestinal tract has been observed by Jones et al. (16) to cause both diarrhea and vomiting. If the stools are bloody or contain pus, further loss of protein is indicated. On the other hand, the interesting report of Shohl tends to support our work (17). In infants suffering from prolonged vomiting and diarrhea and fever, positive nitrogen balances were obtained by the administration of casein hydrolysate either intravenously, orally or both. The outstanding revelation

that the retention of nitrogen was directly proportional to the intake and in reality was as large as those reported for well infants was made.

Peptic ulcer. There were included in this series five cases with peptic ulcer whose nutritional state warranted special consideration. Accordingly, these patients were placed on the high caloric regime along with standard therapy for the ulcer. The hourly dietary schedule (table 1) was combined with the orthodox treatment of non-soluble antacids to yield an energy value in excess of 5000 calories derived from 150-250 grams of protein, 150-250 grams of fat and 600-800 grams of carbohydrate. The program extended from 16 to 21 days. The history of these patients indicated a weight loss of 14 to 30 pounds generally due to the rigors of combat. The weight gain ranged from 8 to 16 pounds. Palmer has stated that it is always desirable to restore the peptic ulcer patient to his normal weight and nutritional state.

MALNUTRITION

For the purpose of this study, malnutrition is defined as a patho-physiologic state in which the intake of food has been insufficient to meet the current metabolic demands of the body. In our experience, malnutrition has appeared in three different patterns. The first type is exemplified by the soldier who fails to take his rations because of the stress and strain of combat. A second group is typified by the prisoner of war to whom sufficient food was not available to meet his metabolic demands. Lastly, is that large category of hospital patients whose metabolic requirements are greatly increased by illness or injury.

The following case resume illustrates the first type of malnutrition: A technical sergeant of an armored division was admitted to this hospital complaining of progressive weakness and fatigue. During five consecutive months of combat, he had consumed no more than one or two portions of the rations issued.² There resulted a weight loss of approximately 25 pounds. For the first time in his life, he developed occasional precordial pain, palpitation of the heart and dyspnea on mild exertion. On physical examination, the principle finding was a moderately debilitated appearance and cold, sweating hands and dermatographia were noted. Laboratory and roentgen observations failed to reveal the presence of organic disease. Shortly after admission to this hospital, atypical pneumonia developed which accentuated the preexisting symptomatology. The attending ward officer properly evaluated this soldier's prime need: Nutritional rehabilitation. Accordingly, he was transferred to this service for the controlled hourly feeding regime. The soldier gained 9 pounds during the first week on high caloric feeding. Interestingly enough,

² The results of a comprehensive field survey of United States Army, C, K and 10-in-1 rations indicate that they are generally highly acceptable in meeting the strenuous physical demands of the soldier (18).

all complaints vanished as he gained strength and weight. After 36 days, he returned to full combat duty, having gained a total of 18 pounds.

The second type of malnutrition discussed here is illustrated by the case of a liberated American prisoner of war. He relates that during his confinement of $2\frac{1}{2}$ months, the rations available each day to him consisted of one bowl of flour soup, one slice of bread and frequently three small potatoes. The caloric content of this intake yielded approximately 328 calories. During the imprisonment his weight had dropped from 157 to 120 pounds. The state of debility was of such severity as to necessitate transportation to this hospital by litter. The physical examination revealed emaciation, pallor and muscle wasting. Within the hour of admission, a high caloric general diet (see table 1) was instituted. The diet was well tolerated from the beginning and on the third day amounted to 7000 calories. He regained 29 pounds in 30 days. Upon discharge, he was symptom-free and had returned to his former state of well-being, weighing 149 pounds.

The mode of feeding to be employed in such cases still appears to be a moot point. Unquestionably, the institution of a full diet in large quantities as we have done in the above patients is novel. The view most commonly held is one similar to that of Jackson: "Even in the initial stages of treating inanition by administering highly nutritious diets, difficulties may be experienced in that the food taken in may not be digested on account of concomitant atrophy of the alimentary tract glands" (19). The prompt appearance of diarrhea after eating is a deterrent to many. Our experience with high caloric feeding in the presence of diarrhea demonstrated that the prime attention should be given to the nutritional status (17).

The third type of malnutrition may be present during any illness or injury and is typified by a soldier who was treated in this hospital for a severe shrapnel wound of the back. Upon recovery from the battle injury, he was unable to participate in the rehabilitation program because of weakness and fatigue. He was 20 pounds below his normal weight level. After 21 days of high caloric feeding exceeding a daily average of 4200 calories, he gained 10 pounds and withstood the rehabilitation program well.

Comment. Loss of body mass (weight) is one of the direct causes of reduced metabolic activity. From this arises weakness and fatigue which all the soldiers demonstrate so well. Whether the autonomic signs seen in the first patient have a similar origin cannot be stated with certainty. Yet, these effects have been reported in vitamin B complex deficiency. It is of significance that such symptoms were alleviated with the restoration of a normal nutritional state.

According to a well-known war correspondent, an inadequate food intake is the rule under combat conditions. "Each night, enough canned rations for

three meals were brought up, but when the men moved on after supper, most of them either lost or left behind the next day's rations, because they were too heavy to carry. But they said when they were in battle and excited, they sort of were on their nerve. They didn't think much about being hungry" (20). The ensuing loss of efficiency of such a soldier is very likely attributed to the more obvious effects of combat. Only when a more tangible wound or illness supervenes do the ravages of this type of chronic malnutrition appear. These are manifested by an unduly prolonged convalescence and failure of the individual to regain the previous physical state upon recovery from the wound or illness.

In short, chronic malnutrition frequently exists in a subtle state. It is often an elusive entity which masquerades in the guise of a battle injury, acute illness or combat exhaustion. The condition is not often overt and will be diagnosed only by careful scrutiny of the dietary history. The alleviation of malnutrition in the presence of battle injury or disease is a challenge to our therapeutic abilities. The weapon which we have developed to this end is the high caloric feeding program.

CONCLUSION

A survey of patients arriving at this hospital revealed that malnutrition is a finding that frequently coexists with other war casualties. Recognition of this fact led to the development of a feeding regimen designed to rectify the deficient nutritional status of these sick and injured soldiers. The prescribed dietary consisted of the equivalent of 5000 or more calories per day, derived from 150-250 grams of protein, 600-800 grams of carbohydrate and 150-250 grams of fat. This quantity of food was administered to the patients in the form of three regular meals augmented by hourly feedings from 0800 to 2100 hours. To insure and encourage the ingestion of the prescribed food, we trained a special staff. They recorded in household measures the amounts of food consumed at each feeding and subsequently computed the daily caloric equivalents. These findings and the weight of each patient were recorded on the chart.

Contrary to prevalent opinion, such a regimen has proved practicable. Anorexia and nausea have been accepted as a challenge. The insistence that the food be ingested overcomes these obstacles within 48 hours, at the same time proving the feasibility of ingesting, digesting and absorbing sufficient food to meet any demand. Hence, in our patients, parenteral supplementary therapy was not deemed necessary.

The series of cases reported in this study included the following diagnoses: Acute surgical conditions, acute infectious hepatitis, chronic recurrent malaria, neuropsychiatric states, gastrointestinal diseases and malnutrition. The

high caloric regimen constituted a major part of the treatment of each of these individuals. As a result, the patients presented a normal state of nutrition at the termination of the disease or injury. The excellent nutritional state attained was evidenced by weight gain, absence of weakness and fatigue and a restored sense of well-being.

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PROBLEMS IN THE ETIOLOGY OF PEPTIC ULCER: THE RESISTANCE OF THE GASTROINTESTINAL TRACT TO THE DIGESTIVE ACTION OF ITS OWN SECRETIONS

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INTRODUCTION

Closely bound up with the problem of the etiology of peptic ulcer is the question "Why does not the stomach digest itself during life?" In a broader sense how can we account for the resistance of living tissues to digestion by their own ferments? This question presented itself to early physiologists as a natural consequence of their observation that the ingested food was attacked and liquefied by the digestive enzymes.

A number of the pioneers in the study of digestion devised ingenious experiments in an attempt to solve the enigma of the resistance of the stomach to autodigestion during life. This subject assumed more than merely academic importance once "peptic" ulcer came to be recognized as one of the most common digestive ailments of man. And today, there are additional questions relating to the effect of digestive secretions on living tissue which require our attention if we are to achieve an understanding of the fundamental phenomena concerned in the onset and course of gastroduodenal ulcerative disease. We propose, therefore, to examine the older theories in the light of present day knowledge, and to review some of the more recent data which bears on this problem.

THEORIES ON THE RESISTANCE OF LIVING TISSUE TO DIGESTION

1. *Hunter's theory of the "living principle."* In 1772, John Hunter (1) attempted the first explanation of the resistance of the stomach to autodigestion. He stated that "animals, or parts of animals, possessed of the *living principle* when taken into the stomach, are not the least affected by the powers of that viscus, so long as the animal principle remains."

Aside from the fact that this concept was too vague to provide a workable theory, the fallacy of Hunter's assumption was demonstrated in 1856, when it was shown that gastric secretion digested the leg of a living frog (2) or the ear of a living rabbit (3).

2. *Bernard's theory of the protective action of the epithelium.* Bernard (2) maintained, in essence, that the stomach does not digest itself because pepsin

* A lecture delivered by A. C. Ivy before the Academy of Medicine of Buffalo, New York.

is not absorbed by living cells and because the mucus and mucus-secreting cells of the surface are continuously renewed. That pepsin is not absorbed by the uninjured living cell has been demonstrated (4) by modern methods; when the cells are injured, pepsin may be absorbed, but will not be active unless the acidity is adequate.

Bernard did not consider adequately the acid factor, probably because he believed lactic acid, a weak acid, was the acid produced by the gastric glands.

In 1886, after hydrochloric acid and pepsin had been shown to be present in gastric juice Frenzel (5) performed the following experiment. One leg of a frog was immersed in 0.2 per cent HCl and the other leg in a pepsin-0.2 per cent HCl solution. After incubation for 1.5 hours the leg immersed in the pepsin-HCl solution was digested to the bone; the other leg was not injured. Frenzel concluded that pepsin augments the injurious action of acid. Matthes (6), in 1893, performed some experiments which led him to believe that the cells were injured by acid and then digested by pepsin. Today, it is well known that pepsin simply catalyzes the hydrolytic action of hydrochloric acid in regard to specific peptide bonds. Thus, the presence of pepsin in an acid solution increases the rate at which a dilute solution of acid hydrolyzes protein, or lowers the concentration of acid which causes hydrolysis in a fixed period of time. From a practical viewpoint, since pepsin is not known to be absent from gastric juice containing acid, the critical level at which injury is likely to occur depends more on the concentration of acid than of pepsin.

3. *Harley's theory of the protective action of mucus.* Bernard assumed, but did not prove, that mucus and the mucous epithelial cells offer a barrier to digestion. In 1860, soon after Bernard published his theory, Harley (7) demonstrated the importance of the layer of mucus secreted by the surface epithelium. He found that "if a stomach be divided into two parts and from one of the halves the mucus be carefully removed . . . while the other half is left intact, it will be found, on making each into a sort of bag, and filling it with pure gastric juice, that a few hours exposure to an elevated temperature will suffice for the solution of the half from which the mucus was removed, whereas the other . . . will remain unacted upon." In 1867, Schiff (8) found that when pieces of excised portions of the stomach were exposed to peptic digestion, the surface epithelium, which contains mucin, was more slowly digested than the muscularis. He also found that a piece of meat separated from gastric juice by a layer of mucus was not digested in 10 hours. Since then it has been found that acid and pepsin diffuse slowly through gastric mucus (9), that mucus inhibits and is resistant to peptic digestion (10), and that it possesses some neutralizing and buffering capacity (11).

4. *The Virchow-Pavy theory of the neutralizing and nutritive function of the blood supply.* In 1853, Virchow (12) explained the origin of ulceration of the

stomach on the basis that "as soon as the customary circulation to the stomach is interrupted, there also are lacking the possibilities of the usual neutralization of the inflowing acid by the alkalis of the blood, and corrosion will follow." Pavy (13) in 1863, found that "a patch of mucous membrane may be removed [from the stomach of a dog] and food will afterwards be digested without the slightest sign of attack being made on the deeper coats of the organ." This he attributed to the alkalinity of the blood opposing the action of the acid of the gastric juice.

Pavy's observation that the removal of a patch of gastric mucosa is followed by complete healing has been confirmed repeatedly; however, autodigestion of the stomach does not occur after ligation of almost all of the arteries along the lesser and greater curvatures. When the veins alone are tied, the mucosa at first becomes congested and edematous, and in some instances hemorrhage erosions occur; these, however, heal rapidly. In fact, an acute ulcer produced by excising a piece of mucosa heals in normal time in a stomach in which all the veins have been tied.

The results of such experiments do not show that a good blood supply is of no importance in preventing auto-digestion, because the tying of the vessels to the fundic mucosa immediately abolishes the secretion of acid, and if the blood supply to only a portion of the wall of the stomach is tied the anastomoses are adequate for the maintenance of good nutrition of the mucosa. Carefully designed experiments have not been performed to ascertain to what extent the blood flow must be reduced to cause an increase in the susceptibility of the stomach to acid.

At any rate, the significance of Pavy's work is not that it answers the question why the stomach does not digest itself, but rather that it raises the equally important question why the acid-pepsin does not digest the exposed cells in an area where the gastric epithelium has been removed, or why does the acute ulcer so produced heal rapidly.

5. *Fermi's theory of the biochemical resistance of the living cell.* About the turn of this century, Fermi (14) criticized all the previous theories and proposed the view that living cells resist digestion because of the configuration of the living protein molecule. Digestion, thus, would not occur until the protein molecule is damaged. The sustaining point of his argument, as with Hunter's was the fact that many bacteria and parasites dwell and thrive in the alimentary tract.

Michaelis (15), in 1926, postulated a biochemical resistance but did not consider it to be a function primarily of the protein structure. According to him, "the superficial cell membranes, which regulate the permeability of any cell, seem to consist of some lipoid substance. Obscure and equivocal though this term may be, at least it is not a protein which may be subject to the action of

pepsin. So, the membranes of the mucosa being indigestible, and certainly also impermeable for a molecule of such large size as that of pepsin, will prevent the interior of the cells from being digested as long as the membrane is intact."

This explanation fails to take into account the effect of the hydrochloric acid. It has been demonstrated that the tolerance of the surface epithelium of the stomach and intestine to acid-pepsin, in concentrations even less than those secreted into the gland tubule, is not unlimited. So, there remains the possible deleterious effect of a hypersecretion or an abnormally prolonged gastric secretory response to a meal.

6. *Weinland's theory of antiferments.* Weinland (16), in 1902, extracted the tissue juice of *Ascaris* and found that it possessed "antipeptic" and "antitryptic" activity. He concluded that the "antiferments" rendered it possible for the parasites to resist peptic and tryptic digestion. Danilevski (17) and Hensel (18) made the same observation but did not refer to the phenomenon as being due to an antiferment because it still occurred after boiling.

It is now known that many substances including peptones and albumoses may inhibit peptic and tryptic digestion. Pepsin cannot produce an anti-pepsin in an immunological sense because pepsin is denatured at the alkalinity of blood. An antitrypsin and an antipepsinogen can be produced, however, because they are not denatured by the alkalinity of blood (19). A trypsin inhibitor of polypeptide nature has been crystallized from an extract of pancreatic tissue (19). A pepsin inhibitor is produced when pepsinogen is converted to pepsin, but this inhibitor does not act at a pH of 4.0 or less (19). The inhibitor of pepsin, present in the serum which exudes from an acute ulcer, loses its activity when the pH falls below 4.0, so that it is unlikely to play an important role in protecting the damaged mucosa in the presence of any high degree of free acidity.

Comment. While it is evident that no single theory has been adequate to explain all of the observed facts regarding the resistance of the gastrointestinal tract to autodigestion, the investigations arising out of these theories have provided new information. The knowledge we have thus gained permits us to present here the facts which any new theory will have to take into account.

FACTORS CONCERNED IN THE RESISTANCE OF THE GASTROINTESTINAL TRACT TO DIGESTION

1. *Resistance of the gastric gland.* The evidence now available shows that acid and pepsinogen are secreted simultaneously. The acid is secreted by the parietal cells and the pepsinogen by the chief cells. The chief cells are concentrated at the base of the gland tubule, the parietal cells near the apex or neck of the tubule. The parietal cell has an intracellular canalicular apparatus which communicates with the lumen of the gland tubule. This feature of the

parietal cell presumably increases its surface to facilitate the elimination or formation of the acid. It is to be noted especially that the acid is formed by one cell and pepsinogen by another cell.

All the evidence indicates that the hydrochloric acid formed by the parietal cell has a concentration of 0.58 per cent, or a pH of 0.83. This concentration of acid is certainly present in the gland tubule, and a greater concentration of HCl is not formed by the cell. Thus, it is obvious that the cells lining the gland tubule are not damaged by a 0.58 per cent HCl solution. It is known that cells in general tend to be impermeable to strong acids such as hydrochloric acid until a toxic concentration is reached. However, it has been reported that 0.4 per cent HCl introduced into the stomach of cats and dogs will cause acute ulcers within 3 days. If this is true, (a) the cells lining the gastric tubule are better adapted to acid than the surface epithelium or (b) the acid as it is formed is rapidly discharged from the tubule, or (c) the gland alternates between a period of secretion and recovery.

In the experiments in which 0.4 to 0.6 per cent hydrochloric acid is kept in continuous contact with the lining of the stomach, the injury first occurs in the pyloric rather than the fundic mucosa. Thus, the surface epithelium of that portion of the gastric mucosa which forms acid is better adapted than that which does not form acid. Since studies on the formation and secretion of acid by the gastric tubule has provided no satisfactory evidence showing that acid is rapidly discharged from the tubule or that when the gland is continuously stimulated it does not secrete intermittently, it would appear that the cells lining the tubule tolerate more or less continuous contact with an HCl solution of 0.58 per cent. For example, the continuous subcutaneous administration of histamine at the rate of 1.5 mg. per hour of the base night and day to the dog produces ulcers in 2 or 3 days. However, these ulcers do not occur in the fundic mucosa; they occur in the esophageal, pyloric and especially the duodenal mucosa.

We do not know whether the pepsinogen is activated while in the gastric tubule. The exact rate of activation of pepsinogen at body temperature has not been determined; at room temperature it is activated in a few minutes. If the pepsinogen is not activated while in the gland tubule, then pepsin does not exist in the acid secretion in the tubule. If pepsin is present there, it cannot affect the cell membrane, according to Northrop, until the membrane is injured by the acid. Hence, pepsin does not have to be given special consideration in answering why the gland tubule is not digested. *Pepsin only facilitates digestion after the cell had been injured by any means.*

Why the cell membranes of the cells lining the gastric tubule tolerate a 0.58 per cent HCl solution is conjectural. They appear to be especially adapted to that end. Their cell membranes may contain more lipid or some

other material resistant to acid, but this would have to be demonstrated by appropriate methods. It should be pointed out that only a portion of the cell surface is exposed, and this surface is subject to being continuously renewed as long as the nutrition of the cell is adequate. This however, is true of all cells, and does not in itself explain the apparently high tolerance of the cells of the gastric tubule for acid.



FIG. 1. Showing no effect of the dropping of N/10 HCl on the mucosa of the pyloric portion of the stomach through a 23 gauge needle for 0.5 hr. at the rate of 120 drops per minute.

2. *The resistance of the surface epithelium.* A fact demonstrated repeatedly, and easily confirmed, is that there is a gradient of susceptibility to acid injury in the gastrointestinal tract. The farther away the mucosa from the source of acid formation, the less the resistance of the surface epithelium to injury by acid. This is demonstrated clearly in the accompanying photomicrographs. A tenth-normal solution of HCl was allowed to drop for 30 minutes through a 23 gauge needle at the rate of 120 drops per minute on the pyloric, duodenal, and jejunal mucous membrane of an anesthetized dog.

Figure 1 shows the result on the pyloric mucosa, near the sphincter; there is

thinning or absence of the layer of mucus, but no impairment of the tips of the glands. By contrast, the mucosa on the duodenal side of the sphincter (figure 2) shows desquamation of the surface epithelium, leaving the tips of the villi denuded but otherwise intact. Finally, the mucous membrane of the first loop of jejunum (figure 3), under the same degree of acid trauma, suffered desquamation of the epithelium, disruption of the villi, marked hyperemia and extravasation of blood.

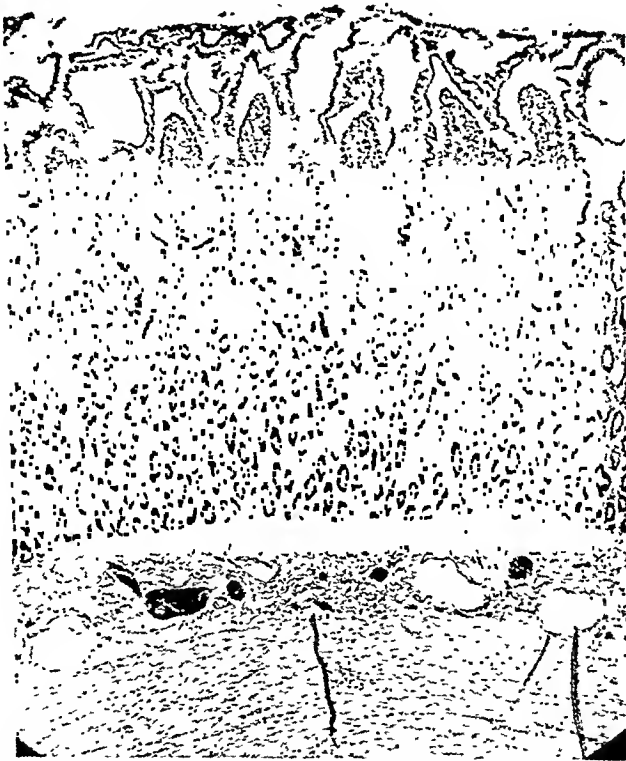


FIG. 2. Showing injury of the mucosa of the duodenum caused by the procedure given in the legend for figure 1. The tips of the villi are denuded but otherwise intact.

This gradient of susceptibility from the fundic mucosa downward in the alimentary tract appears to be one of the principal phenomena to be accounted for in attempting to understand the resistance of the surface epithelium. The factors upon which we may speculate at present are the structure of the epithelial cells and the role of the external secretions of the alimentary tract.

The surface epithelium of the mucosa of the fundic and of the pyloric portions of the stomach consists of a continuous layer of mucous secreting glands. In

so far as mucus is concerned, it appears that the pyloric mucosa should be better protected than the fundic mucosa. Inspection of the living gastric mucosa indicates that the fundic mucosa has a better blood supply, a view which is supported by anatomical studies. Whether this entirely explains the greater resistance of the fundic mucosa is uncertain. Chemical differences in the



FIG. 3. Showing injury of the mucosa of the first part of the jejunum caused by the procedure given in the legend for figure 1. The epithelium of the villi is desquamated, the villi are disrupted and there is marked hyperemia with hemorrhage.

mucus or in the cell membranes may exist, a possibility that we are uncertain of at present.

The duodenal mucosa is not covered with a continuous layer of mucous secreting cells. But, the first few inches of the duodenum contain a good complement of Brunner's glands, which secrete an alkaline mucus or mucoid fluid; and goblet cells are interspersed among the cells of the surface epithelium. In addition, alkaline pancreatic juice and bile may regurgitate to the level of the duodenal antrum. Also, some have suggested that the blood supply of

the first inch of the duodenum is not so great as in the fundus of the stomach. The chief difference, however, and one that is not subject to argument, is the lack of a continuous mucous secreting surface epithelium. Hence, it is not surprising that when acid is continuously poured over its mucosa by perfusion or as the result of the continuous injection of histamine that the duodenum is usually injured before and to a greater extent than the gastric mucosa.

The secretion of Brunner's glands would seem to be important in the protection of the mucosa of the duodenal antrum from acid injury. In the dog, 12 cc. of Brunner's juice may be obtained from the first inch of the duodenum in one hour. Its flow is stimulated by the local application of dilute acid and by a hormone mechanism, the hormone being present in appropriately made extracts of the upper intestinal mucosa.

The jejunal mucosa contains only goblet cells and a few scattered Brunner's glands. To this extent it is poorly protected from acid injury as compared to the stomach and duodenum.

The greater susceptibility of the jejunum and the probable importance of the Brunner's secretion is illustrated by the following experiment. When the jejunum is anastomosed, end-to-end, to the first 1.5 inches of the duodenum, and the pancreatic juice and bile diverted to the lower ileum, ulcers occur in the jejunum and not the duodenum. Unless there is a chemical difference in the cell membranes of the duodenum and jejunum, the difference in susceptibility to ulcer formation can be due only to the Brunner's secretion.

Pancreatic juice protects the duodenal mucosa, because when the pancreatic juice does not flow into it duodenal ulcers form in 10 or 15 per cent of dogs. Pancreatic juice and bile protect the jejunum, because when a simple gastro-jejunosomy is performed only 10 or 15 per cent of dogs develop jejunal ulcer, whereas, with the same operation and the diversion of pancreatic juice and bile to the lower ileum, 98 per cent develop ulcer.

3. *The resistance of muscle cells, connective tissue, and fibroblasts: or the resistance of a chronic ulcer to healing.* It is well known that ulcers of the stomach and duodenum can persist for weeks without perforating. It is also known that acute ulcers produced in the stomach and intestine in man and animals (1.5 to 2.0 cm. in diameter) heal in 3 or 4 weeks. In such instances smooth muscle, connective tissue, and fibroblasts are exposed to the gastric juice or contents. In contrast to most food, they are living cells receiving a blood supply. This raises the question of what is known regarding the resistance of such cells to solutions of a strong acid such as HCl.

Muscle cells are killed when exposed to a solution of HCl having a pH of 4.0, which is the pH at which "free acid" is said to exist in gastric juice. As is well known, white and elastic connective tissue are resistant to acid and are

difficult to digest. Fibroblasts do not grow in tissue culture when the acidity of the medium is more than pH 5.0 (20).

These observations indicate that an acute ulcer should penetrate to the serosa rapidly and that it should not heal as long as muscle cells and fibroblasts are exposed to "free HCl." Since such ulcers rarely penetrate and usually heal, factors must operate which prevent them from being exposed to "free acid". Such factors as the following are probably concerned. The transudation of plasma and the formation of a fibrin coat would serve to buffer acid and protect the underlying cells. The fibroblasts begin to proliferate in several hours and their exposed surface may be renewed. The outer layer of fibroblasts may be killed, which would provide protection for the underlying fibroblasts. When the free acid is absent, being buffered by food, the fibroblasts would not be injured. During the period between meals, the secretion normally is low in volume and the acid which actually comes into contact with the base and margins of the ulcer can be buffered by transudate and the outer film of cellular detritus. Either such factors operate to protect the fibroblasts, or fibroblasts growing *in vivo* are more resistant to acid than those growing *in vivo*, because we know that acute ulcers usually heal in 3 or 4 weeks although free acid can be found in the stomach at least during 16 hours out of the 24 hour period.

The mucoïd cells which grow out from the margins to cover the granulation tissue (fibroblasts) must be resistant to fluids having an acid reaction greater than pH 4.0. The resistance of proliferating mucoïd cells to acid has not been studied by the method of tissue culture. If these cells were found to be as resistant to acid as surface epithelial cells, the explanation for healing in the presence of some free acid in the stomach most of the 24-hour period would appear to be complete.

The literature on the healing of peptic ulcer, although unsatisfactory to the extent that an adequate clinical study has not been reported, had led us to suspect that *there is usually little difference between the potential rate of healing of the acute ulcer of a non-ulcer patient and the "chronic" lesion of an individual with peptic ulcer.* We now have available the results of a well controlled series of observations (21) which prove conclusively that the crater of a gastric or duodenal ulcer disappears in the majority of cases within six weeks after the patient is placed on strict ulcer management, without any "specific" adjunctive therapy.

Therefore, the essential difference between an acute ulcer in a dog or man, and the ordinary peptic ulcer in the average patient is that in the former, conditions favorable for healing are present, while in the latter they are not. In terms of the foregoing discussion, the ulcer patient is one with either a normally resistant upper gastrointestinal mucosa subjected to excessive trauma from abnormally high gastric secretions, or a less resistant mucosa susceptible

to injury at normal acid-pepsin levels. If this is the case, the therapeutic desideratum is to find a physiologically innocuous and non-destructive method to control secretion or to improve the resistance and proliferative activity of the cells; for then, the acute lesion from which all chronic lesions originate should heal in normal time, and recurrences should be prevented.

CONCLUSIONS

The stomach does not digest itself when the circulation of its mucosa is adequate, when the tolerance of the cells to acid-pepsin is not exceeded and when the nutritional or metabolic condition of the subject is adequate for the regeneration and proliferation of the cells of the gastric mucosa and for mucus secretion.

The gastrointestinal mucosa displays a gradient in its susceptibility to injury by acid-pepsin. The farther the mucosa is removed from the site of formation of acid-pepsin the greater is its susceptibility to damage. In the upper gastrointestinal tract special mechanisms help to account for the gradient of susceptibility (mucus secretion, Brunner's gland secretion, pancreatic juice and bile). In the lower intestine the increasing susceptibility of successively lower segments must be attributed to the lack of adaptation of the lining cells to acid-pepsin and a decrease in secretion of intestinal juice. The nature of this adaptation appears to depend on the cell membrane and the extent of its resistance to acid and alkalis.

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THINGS TO DO IF CANCER OF THE STOMACH IS OFTENER TO BE CURED

REPORT OF AN INSTRUCTIVE CASE

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Although the lessons taught by the following short case report have been pointed out many times before, the experience of consultants everywhere today shows that there still is much need for repeating such statements as: "beware of the short history of ulcer in an older person," "don't be reassured by normal gastric acidity," "don't be reassured by the roentgenologic diagnosis of gastric ulcer," "don't be reassured when under treatment the ulcer disappears and the patient gets well and fat" and "don't start medical treatment if the patient is going to get out from under your control."

The man whose case is here reported now owes his good chances of survival to the fact that his son is a wide-awake and well-informed physician, who sent him quickly for roentgenologic study the day symptoms appeared, and then kept forcing him to return for check-ups every few weeks. Actually, I would have preferred to see the man at intervals shorter than they turned out to be.

An active, unusually young-looking man of seventy-six years came to the Mayo Clinic in August, 1945, with the story that some six weeks before, after a lifetime of good health and excellent digestion, he had begun to get nauseated and to vomit if he exerted himself physically. He had practically no indigestion after eating but was somewhat conscious of his epigastrium; he had lost some of his appetite and he had lost a little weight. He had also begun to be constipated. There was no symptom or sign of heart disease to explain the nausea on exertion.

Roentgenologic examination at home had showed a small prepyloric crater which was assumed to be malignant because of the short history.

At the Mayo Clinic physical examination showed nothing significant. The roentgenologists confirmed the presence of a prepyloric ulcer and wisely refused to hazard a guess that it was not malignant.

The hemoglobin reading was 13.3 gm. per 100 c.c. of blood and the blood sedimentation rate was 4 mm. in an hour (Westergren). Gastric analysis showed 70 units of free acid and 80 units of total acid, readings most unusual for a man of his age. There was no sign of blood in the gastric contents. Under medical treatment the man immediately became comfortable and in five weeks had gained 9 pounds. Re-examination then showed no sign of an ulcer but persistence of what looked like antral spasm.

With misgivings I allowed the man to continue the ulcer diet for another five weeks, during which time he felt fine and gained 2 more pounds. Then the roentgenologic

report was "annular lesion at the pylorus, probably malignant." The man went home to arrange for operation, and on his return three weeks later, roentgenologic examination left no question about the presence of a carcinoma. At operation the surgeon found a grade 1 adenocarcinoma of the pylorus, 4 by 2 by 1 cm. in size. No glandular involvement was found.

SUMMARY

The obvious lessons are (1) that a short history and a gastric "ulcer" in a person well past middle age usually mean cancer, (2) that the results of gastric analysis are of little diagnostic value and (3) that great improvement under medical treatment and the disappearance of the crater should not lead to any relaxation of vigilance.

THE CONSISTENCY, OPACITY, AND COLUMNAR CELL CONTENT OF GASTRIC MUCUS SECRETED UNDER THE INFLUENCE OF SEVERAL MILD IRRITANTS^{1,2}

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INTRODUCTION

Beaumont (2) summarized his observations on the appearance of the normal resting gastric mucosa as "soft, or velvet-like . . . and constantly covered with a very thin, *transparent*, viscid mucus lining . . .", but on the same page (p. 103) he stated that the mucus of the stomach is "viscid, albuminous, *semi-opaque*" (*italics ours*). This discrepancy suggests that the appearance of gastric mucus may not be constant, even in the normal stomach—a view which has been borne out by the observations of numerous subsequent investigators on the acid-free secretion from whole stomachs or pyloric pouches of dogs or cats. Such material has been variously described as thick, viscous, jelly-like, viscid, mucilaginous, or tenacious. When it is obtained as a spontaneous secretion, most authors agree, the material is clear and transparent (4, 6, 8, 12, 19, 21, 22); in contrast with this, however, Schemiakine (26) and Takata (28) reported clumps and flakes of mucin in suspension, Grant (10) obtained a product which was opaque and greyish-white, and Baxter (1) described his material as "whitish." Concerning the character of mucus secreted in response to stimulation, the following observations have been reported: weak electrical excitation of the vagus yielded a transparent product (10); clove oil in 5 percent aqueous emulsion, water saturated with ether (5), and saline solutions of purified alkyl sulfates (27), each gave a clear or only slightly opalescent secretion; but electrical stimulation of the splanchnics (1), 60–95 per cent alcohol, and 1 per cent acetic acid (10) all yielded opaque, whitish mucus. Concerning the occurrence of variations in macroscopic appearance of the material which may be observed from time to time with the same stimulus, the aforementioned reports contain no evidence at all, and only one of these investigators (10, 11) has discussed the microscopic appearance of such specimens.

In the present work, an attempt has been made to evaluate statistically, and to account for, the incidence of specimens possessing different degrees of opacity

¹ Preliminary reports of this work were presented before the Federation of American Societies for Experimental Biology in 1941 (17) and the American Gastroenterological Association in 1944 (15). Some of the observations were demonstrated at the Graduate Fortnight of the N. Y. Academy of Medicine in 1943.

² This investigation was supported in part by grants from The Anna Fuller Fund, Wyeth Inc., and The United Hospital Fund of N. Y.

and consistency, using only native gastric mucus which is free of obvious hydrochloric acid. A microscopic study has been made of the columnar cell content of these specimens, and the results have been correlated with their gross physical characteristics. To obtain the mucus, various stimuli were employed, and the several characteristics of the secretion have been studied in reference to this variable as well.

PROCEDURE

The mucus used in this study was collected in systematic experiments with 7 dogs, having Pavlov or Heidenhain pouches prepared from the gastric corpus. Also included are specimens of mucus obtained from about a dozen other pouch dogs which were used for only occasional experiments of the same kind.³ The duration of the entire study extended over a period of about five years. It should be noted that almost all of the investigations in other laboratories, cited above, were performed with pouches of the pyloric antrum, or with isolated whole stomachs which included pyloric mucosa—rather than with pouches of the corpus or fundus of the stomach alone.

The experimental technique was as follows: The dog was deprived of food for 18–24 hours preceding the experiment. During the latter half of the investigation, we adopted the practice of giving the animal 15–20 cc. of castor oil about 6 hours after removing the food crock from the cage, in order to aid in establishing an acid-free condition in the pouch at the beginning of the experiment. On the following morning, the animal was suspended according to the technique usually employed in this laboratory for the collection of gastric juice from pouch dogs, and “spontaneous” secretion was collected continuously for successive half-hour periods. If the first specimen so obtained had a pH of less than 6.0, this preliminary collection was continued until the pH was clearly above this level. In case the animal failed to yield any secretion from the pouch, the material adhering to the eyes of the collecting catheter was used for the pH determination. It happened occasionally that a dog continued to yield secretion with a pH below this arbitrary limit for 3 or 4 hours. When this happened, the experiment was discontinued for the day. In none of these experiments was there any indication that the pretreatment with castor oil influenced the rate of flow or the character of the mucous secretion, except for a striking reduction in the incidence of free acid in the “spontaneous” secretion.

When it was finally established in this way that the pouch was free of obvious parietal secretion, the experiment proper was started. For chemical stimulation, the animal was removed from its sling and the collecting device was re-

³ A few specimens of “spontaneous” mucus secretion were collected also from dogs provided with patches of exteriorized gastric mucosa (prepared by Doctors L. Druckerman and J. Bandes for another investigation).

placed by a Pezzer (mushroom) catheter—no. 18–22 Fr.—which had been cut down to a length of 4–5 inches. By means of a syringe attached to the catheter the stimulating fluid, at a temperature of about 40°C., was then slowly injected into the pouch. The volume of stimulus was such as to fill the pouch completely without the application of any considerable pressure to the plunger of the syringe. In general, this volume was determined by the tonus of the pouch wall as well as the rate of injection; at no time did it exceed 55 cc. The fluid was withdrawn after 5 minutes and immediately reinjected, thus bringing a fresh portion of the material into contact with the mucosal lining. This withdrawal and reintroduction was repeated after a second 5-minute period. When water saturated with ether was used as the stimulus, a fresh portion of solution was employed for each reinjection in an effort to maintain the concentration of the volatile solute at saturation. Following the third such interval the withdrawal was permanent; the dog was returned to the sling, the collecting device reinserted, and the collection of mucus started. In the case of the clove oil experiments, only two such 5-minute intervals were employed. The first specimen always contained a large proportion of the stimulus, and for this reason it was discarded. After 30 minutes, however, this fluid seemed to have been washed away completely by the mucus secretion, and subsequent specimens were retained for examination. The time interval for the collection of each specimen, and its volume, were both recorded; the former was allowed to vary in accordance with the requirements of the particular experiment, and was usually determined by the volume of mucus obtained. Collection was continued until the rate of secretion had fallen to an insignificant value.

Numerous specimens were collected in response to each of the following stimuli: 1 gentle massage of the mucosa for 3–5 minutes, by means of a soft rubber catheter; 2 distilled water saturated with ether (about 6 per cent concentration at 30°C.); 3 five per cent emulsion of clove oil in water, with and without acacia for stabilization of the emulsion; 4 fifty per cent ethyl alcohol; and 5 no stimulus whatever, i.e., “spontaneous” secretion. All of these agents have previously been used by other investigators. In addition to experiments performed in relatively large number with these stimuli, a few experiments were performed with 6 distilled water, 7 isotonic NaCl solution (0.17 N), and 8 hypertonic NaCl solution (0.5 N). Solutions which are known to be mucus stimuli, but which are certain to react chemically with the secretion—like acetic and hydrochloric acids—were not employed in this investigation.

Immediately after collection, the consistency of each specimen was recorded either as *fluid* (even when its viscosity was visibly greater than that of water), *viscous* (when it resembled egg-white or jelly, either stiff or soft), or *mixed* (when it was an obvious mixture of both types). The degree of turbidity was noted as *opaque*, *translucent*, or *transparent*. Because the difference in optical density between the last two of these is relatively slight, as compared with the

first, transparency and translucency were tallied together for the statistical purposes of this report and have been designated as *non-opaque*.

Cell content was evaluated by the microscopic examination of smears prepared within a half hour after collection. These smears were made by gently distributing the material on a slide with a smooth glass rod, taking precautions to make a thin smear with a minimum of maceration of the suspended particles. After air-drying, the preparation was fixed by rapid passage through a Bunsen flame, and then treated with Wright's stain by a technique essentially like that of de la Fuente (7). In some cases the microscopic appearance of the specimen was confirmed by examination of a smear stained with toluidine blue for permanent metachromasia (13). Such metachromatically stained smears reveal some structures not discernible in slides stained with Wright's stain, and the results of their systematic study will be presented in a later report. For our present purposes, however, we were concerned with the presence of columnar epithelial cells only. Their density was recorded in the protocols by the arbitrary notation of zero to + + + +; in the tabulation for the statistical analysis, however, these 5 categories were reduced to 2; no cells or very few (0, +), and many cells (+ + through + + + +). A more precise quantitative method of recording cell density was unavailable.

The several characteristics with which we were concerned in this investigation were not studied as a function of the time following application of the stimulus nor of the rate of secretion. Although this procedure is the one usually followed in studies on the acid secretion in the stomach, it has been omitted here because of the apparent lack of regularity and reproducibility in the volume-rate of viscous mucus secretion from experiment to experiment, even when the same dog and the same stimulus are used. Such irregularities result in part from the intermittent movement of the material through the collecting catheter, in consequence of its high viscosity, and in part from irregularities inherent in the secretory response itself. Furthermore, because of the variations in rate of secretion in different experiments, as well as other exigencies, it was frequently found inadvisable to maintain a constant time interval for the collection of individual specimens. For purposes of statistical analysis, the data were grouped according to stimulus, regardless of individual dog. This procedure made it possible to evaluate the relative frequency of occurrence of each characteristic of the mucous secretion, to compare these frequencies for different stimuli, and to study the statistical association of any two of these characteristics.⁴

⁴ The results of the simple frequency analyses according to stimuli may be influenced by the lack of standardization of volume of specimen or duration of its collection. Hence, conclusions drawn from these data must be held subject to adequate corroboration. The contingency correlations, however, are not seriously affected by this lack of standardization and so we consider it justifiable to apply the χ^2 test for the significance of these correlations.

TABLE 1

Frequency and percentage incidence data for consistency, opacity, and columnar cell content of specimens of non-acid gastric pouch mucus obtained with various stimuli

		STIMULI								Totals
		NaCl (0.17 N)	"Spon- taneous"	Massage	Distilled Water	Ethyl Alcohol (50%)	NaCl (0.5 N)	Ether in water (sat.)	Clove Oil (5%)	
Consistency	Viscous	2 13.3%	75 45.7%	17 53.1%	7 58.3%	23 60.5%	9 69.2%	87 70.7%	27 96.4%	247
	Fluid	9 60.0%	58 35.4%	9 28.1%	3 25.0%	6 15.8%	0 0%	9 7.3%	1 3.6%	95
	Mixed	4 26.7%	31 18.9%	6 18.8%	2 16.7%	9 23.7%	4 30.8%	27 22.0%	0 0.0%	83
	Totals	15 100%	164 100%	32 100%	12 100%	38 100%	13 100%	123 100%	28 100%	425
	Order No.	1	2	3	4	5	6	7	8	
Opacity	Opaque	2 20.0%	27 27.0%	3 23.1%	2 33.3%	14 82.4%	6 75.0%	87 83.7%	26 96.3%	167
	Non-opaque*	8 80.0%	73 73.0%	10 76.9%	4 66.7%	3 17.6%	2 25.0%	17 16.3%	1 3.7%	118
	Totals	10 100%	100 100%	13 100%	6 100%	17 100%	8 100%	104 100%	27 100%	285
	Order No.	1	3	2	4	6	5	7	8	
Columnar cell content	Many cells	1 7.1%	30 30.0%	3 27.3%	5 41.7%	30 81.1%	10 76.9%	61 67.0%	19 95.0%	159
	Few cells†	13 92.9%	70 70.0%	8 72.7%	7 58.3%	7 18.9%	3 23.1%	30 33.0%	1 5.0%	139
	Totals	14 100%	100 100%	11 100%	12 100%	37 100%	13 100%	91 100%	20 100%	298
	Order No.	1	3	2	4	7	6	5	8	

* Non-opaque = transparent or translucent.

† Few cells = none or a small number of single cells per field.

RESULTS

Consistency. The incidences of viscous, fluid, and mixed specimens are presented in table 1, with the stimuli arranged in the order of increasing percentage

frequency of the viscous specimens. Data for water, 0.17 NaCl, and 0.5 N NaCl solution, are also included, although the total number of observations in each of these three groups of experiments is relatively small. First in the series of stimuli stands isotonic saline, with a predominance of the specimens—but not all—in the fluid category. At the other end of the series is clove oil, for which practically every specimen is in the viscous category (more than 96 per cent of the total). The other six stimuli yield both viscous and fluid specimens in graded proportions, with a significant percentage in the “mixed” category as well. Some of our experiments, not reported here, afford supportive evidence that clove oil may also yield some of the fluid secretion if this stimulus be used in concentrations of 2 per cent or less.

The order numbers of the stimuli, corresponding to the relative frequency with which they yield jelly-like mucus, evidently bears some relation to the intensity of stimulation. The “spontaneous” secretion and that stimulated by mucosal massage have practically the same percentage incidence. This is not surprising because the former arises in great part from the gentle rubbing of the collecting catheter against the mucosa, and it is therefore mechanical, at least in part, rather than completely “spontaneous.”⁵ The isotonic saline group contains an appreciably lower proportion of viscous specimens than the “spontaneous”; this may be ascribed to the lubricating action of the solution on the surface of contact between catheter and mucosa, coupled with its complete freedom from chemical irritating power. Distilled water, 50 per cent alcohol, hypertonic saline, and ether solution all may be classified as very mild irritants, with a potency which roughly increases in the order given. Likewise, they evoke progressively greater proportions of jelly-like mucus, but the differences among these four frequencies are of questionable statistical significance. The clove oil emulsion is considerably more effective than any of these other agents, both as an irritant and as a stimulus for viscous mucus secretion. In any experiment which yields both fluid and jelly-like material, the latter is secreted immediately after stimulation whereas the former is put out during the latter part of the experiment, when the output is diminishing. The mixed specimens are usually collected during the transition interval, and therefore contain both types of product.

In general, therefore, it may be concluded that all the stimuli here employed give rise to both viscous and fluid mucus, and that the relative frequency of occurrence of the jelly-like secretions increases with the irritating power of the agent as commonly conceived. In other words, potency as a stimulus to the secretion of viscous mucus runs parallel in a general way with potency as a tissue irritant.

⁵ The average rates of secretion in these two categories are approximately the same and extremely low—about 0.2–0.3 cc. per quarter hour.

Opacity. For ease of comparison with the consistency data, the incidence of opaque and non-opaque (i.e., transparent and translucent) specimens is also presented in table 1. As before, isotonic salt solution occupies first position in the serial arrangement of the stimuli (order number 1). Likewise, the clove oil emulsion stands last in the series, all but one of the specimens being markedly opaque (more than 96 per cent). Between these two extremes, the other six stimuli fall in essentially the same order as they do for the consistency data. Thus, distilled water and aqueous ether solution possess the order numbers 4 and 7 respectively in both tabulations. The order numbers for "spontaneous" and massage specimens are interchanged, but the actual percentage values in these two categories (also that for 0.17 N NaCl) differ by so little (4.1 per cent)

TABLE 2

Contingency correlation: opacity and consistency of specimens of non-acid gastric pouch mucus (all stimuli)

		CONSISTENCY			TOTALS
		Viscous	Fluid	Mixed	
Opacity	Opaque	129 45.3%	2 0.7%	36 12.6%	167 58.6%
	Non-Opaque*	51 17.9%	55 19.3%	12 4.2%	118 41.4%
Totals		180 63.2%	57 20.0%	48 16.8%	285 100%
$\chi^2 = 89.2$		$n = 2$		$P < 0.001$	

* Non-opaque = transparent or translucent.

that the difference is void of statistical significance. The order numbers for 50 per cent alcohol and hypertonic NaCl solution are also the reverse of those in the consistency tabulation. The difference between these percentage incidences (7.4 per cent) is somewhat larger than the difference for "spontaneous" and massage specimens, but even this is not great enough to be statistically significant—especially in view of the small number of samples in each of the two groups. Hence, this reversal of order also appears to be unimportant.

In order to establish statistically the validity of this association of consistency and opacity revealed by the order numbers, the data for all stimuli have been combined in a 2 by 3 contingency table (table 2). The total number of specimens (285) represents all those for which both categories of data were available. From this analysis it is evident that almost none of the fluid specimens were opaque (2 in 57 or 3.5 per cent of this subtotal), although more than half of the

total number, irrespective of consistency, belong in this latter category (167 in 285 or 58.6 per cent). The viscous specimens, on the contrary, show a decided tendency to high opacity; of a total of 180 such specimens, 129 (71.7 per cent) fall in the opaque category. The specimens designated "mixed" seem to be similar to the viscous ones in this respect, since the percentage of these which are likewise opaque is 75 per cent (36 in a total of 48). For this correlation table, χ^2 is 89.2 and the number of degrees of freedom (n) is 2; hence P is very

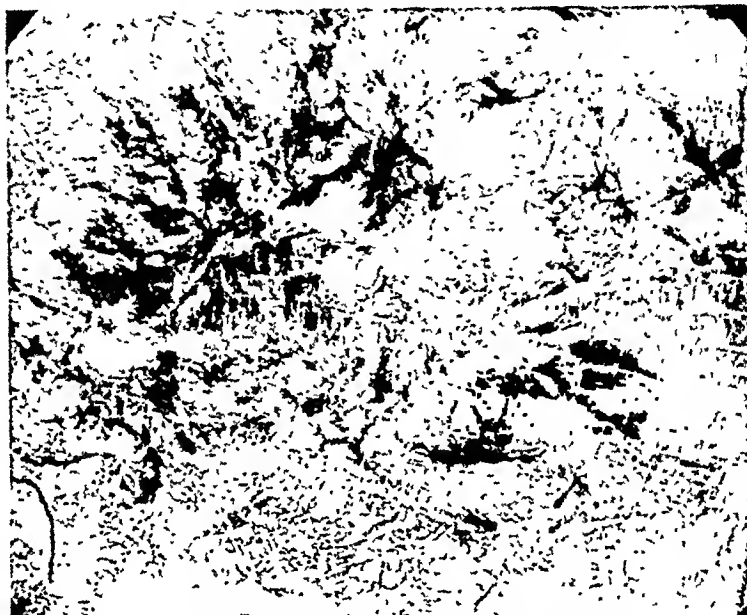


FIG. 1. SMEAR OF GASTRIC MUCUS—NO SUSPENDED MATERIAL

Specimen—#1725
Stimulus—"Spontaneous"
Opacity—Non-opaque
Consistency—Viscous
Stain—Toluidine Blue
Magnification—75 \times

much less than 0.1 per cent, and the statistical significance of the association is beyond question.

Macroscopic examination of the translucent specimens reveals the presence of dust-like particles suspended in a menstruum which may be presumed to be the same as the transparent specimens of like viscosity. Particles large enough to be visible to the naked eye may be present in the transparent material, but so sparsely distributed as to contribute little to the opacity. The opaque specimens likewise contain dust-like particles, in greater density than do the non-opaque specimens, but the larger particles predominate and evidently constitute the main cause of the opacity. These larger particles are solid and irregularly

shaped, with a length which sometimes exceeds 2 mm. In order to establish their identity we instituted the routine preparation and microscopic examination of a smear of each specimen collected—with the following results.

Presence of columnar cells. The microscopic appearance of the mucus smears varies considerably, but always in conformity with a few well-defined patterns. Occasional smears contain virtually no suspended material whatever, as in the photomicrograph of fig. 1. The dark wisps of cloud are areas of

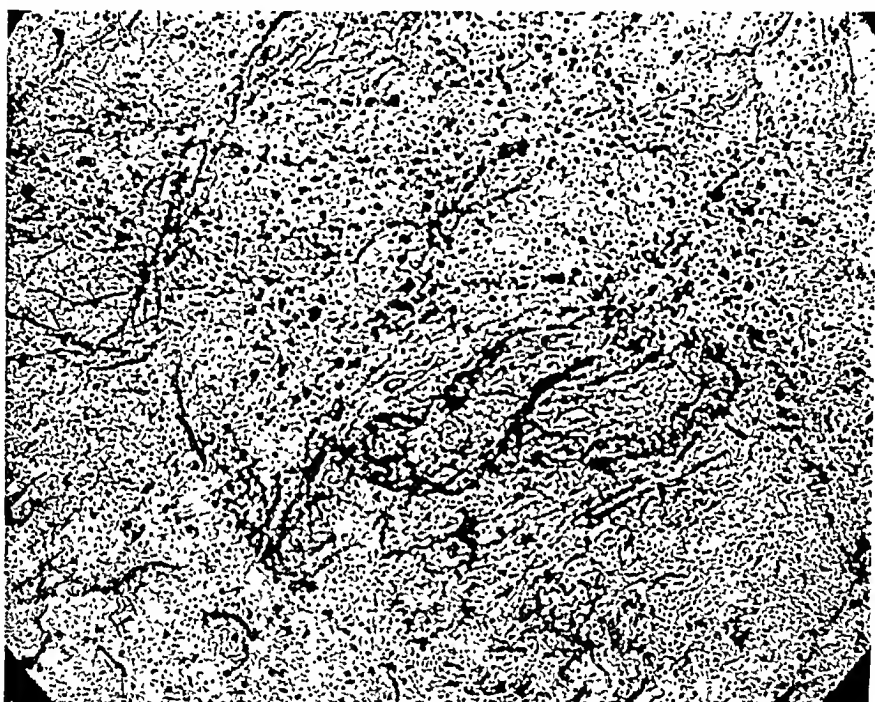


FIG. 2. SMEAR OF GASTRIC MUCUS—CELLULAR DEBRIS BUT NO INTACT CELLS
Specimen—#94.6
Stimulus—NaCl (0.5 N)
Opacity—Non-opaque
Consistency—Viscous
Stain—Wright's
Magnification—75 x

mucus which are a little thicker than the background because of their greater density or viscosity. The fern-like appearance represents only one of several crystal-like structures which we have seen in these smears and which will be reported on elsewhere. Apparently, specimens like the one represented in this illustration consist of more-or-less pure mucous or mucoïd secretion, practically free of cellular material of any kind. Frequently, however, the smear (fig. 2) reveals a substratum of the same character as that depicted in the previous picture, but stippled with minute particles—such as would impart a cloudy or translucent appearance to the specimen if present in relatively small quantities.

Specks which are not in sharp focus are suspended at different levels of the transparent substratum. Some of these particles are cellular debris whereas others may be secretory granules or flecks of mucus; intact cells may be entirely absent, as in this specimen.

More often, however, the photomicrographs reveal wholly intact columnar cells in addition to cells in various degrees of disruption. If the density of such shed cells is relatively small, the smear may manifest extensive cell-free areas, resembling fig. 2. Very often, however, the density of desquamated columnar

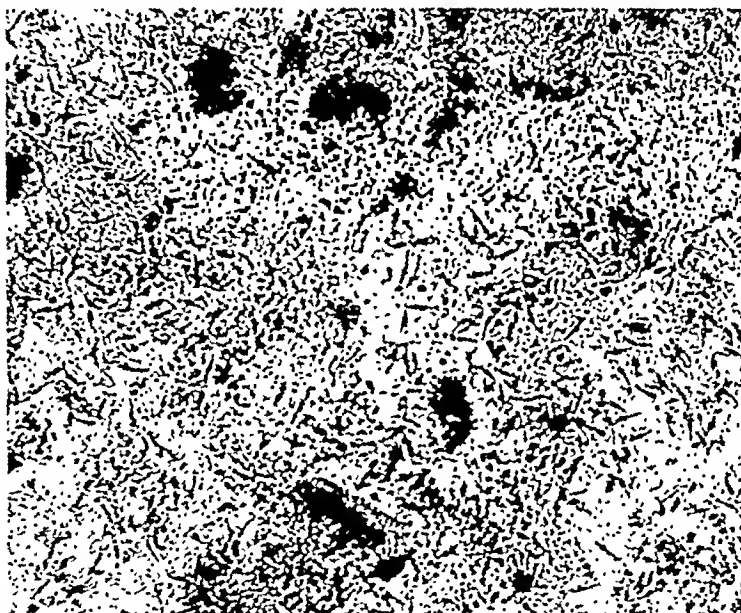


FIG. 3. SMEAR OF GASTRIC MUCUS—COLUMNAR CELLS IN VARIOUS DEGREES OF DISPERSION

Specimen—#163.11
Stimulus—Clove Oil (5%)
Opacity—Opaque
Consistency—Mixed
Stain—Wright's
Magnification—150 x

cells is exceedingly great—as depicted in fig. 3. In such cases the smear may contain not only isolated cells in great numbers but also entire palisades or ranks of intact columnar cells which are held together by their cement substance, and cast off *in toto*. The single cells may be entirely intact, or their thecae may be ruptured during the ejection of their mucus content, or they may have undergone varying degrees of destruction leaving only fragments of theca and cytoplasm attached to the nuclear portion. The sizes of the organized groups vary from only a few cells, as in fig. 4, to a rank as long as that in fig. 5.

Furthermore, these particles may consist of a single layer of cells lying in the same plane, or of several layers which constitute a three-dimensional extension of the fragment of gastric mucosa. Frequently, the ranks of surface epithelial cells are disrupted without extensive dispersal of the individuals—resulting in an irregularly arranged clump of cells, bound together by a mat of extracellular mucin (fig. 6).

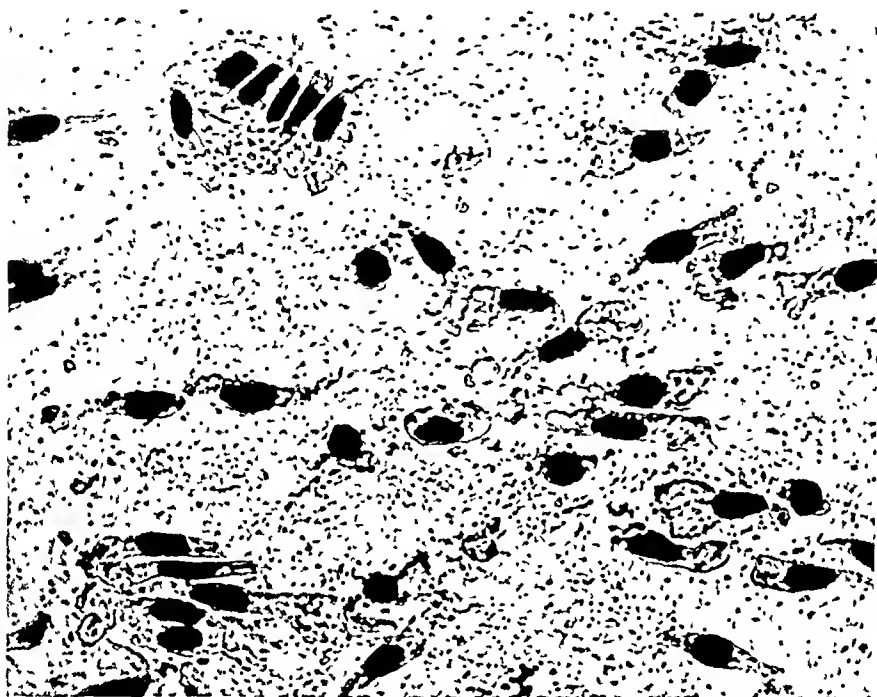


FIG. 4. SMEAR OF GASTRIC MUCUS—COLUMNAR CELLS, ISOLATED AND IN SMALL GROUPS

Specimen—# 169.9
Stimulus—Clove Oil (5%)
Opacity—Opaque
Consistency—Viscous
Stain—Wright's
Magnification—675 x

In view of these variations in columnar cell content, a statistical study was made of the frequency of occurrence of specimens with and without such cells. For this purpose the slides were classified according to two categories: 1—those having no columnar cells at all, or at most a few isolated ones; and 2—those having a considerable number of single cells, with or without intact ranks and clumps. This dichotomy is patently a crude one from the quantitative point of view. In addition, it may be expected that the correlation between the cell density of an entire specimen and that of one or two smears prepared from it will be poor, so that a smear may not always be representative of the specimen of mucus from which it was prepared. In spite of these quantitative uncertainties, a frequency analysis for the percentage incidences of 298 diversely stimu-

lated specimens, based on this dichotomy (table 1), revealed a sequential relation among these stimuli which is nearly the same as for *consistency* and *opacity*. For example, comparing the order numbers for *columnar cells* with those for *opacity*, we find them identical throughout except for the interchanges of 5, 6, and 7. The percentage incidence values for these three stimuli differ by so little among themselves, for the most part, that no statistical significance may be attached to this inversion in order number. Isotonic NaCl and clove oil



FIG 5 SMEAR OF GASTRIC MUCUS—LARGE RANK OR PALISADE OF COLUMNAR CELLS

Specimen—# 163 11
Stimulus—Clove oil (5%)
Opacity—Opaque
Consistency—Mixed
Stain—Wright's
Magnification—675 x

both retain their characteristic positions (order numbers 1 and 8 respectively) as do the group of extremely mild stimuli comprising "spontaneous", massage, and distilled water.

Thus, it appears that all three of these properties of mucus—consistency, opacity, and columnar cell content—vary in essentially the same way, so far as their percentage incidences for the various stimuli are concerned. It therefore becomes necessary to confirm this association of cell content with the other two characteristics by the same method as was used for these two alone. Accordingly, contingency correlation charts similar to that of table 2 were made for the incidence of columnar cells in association with each of the other variates

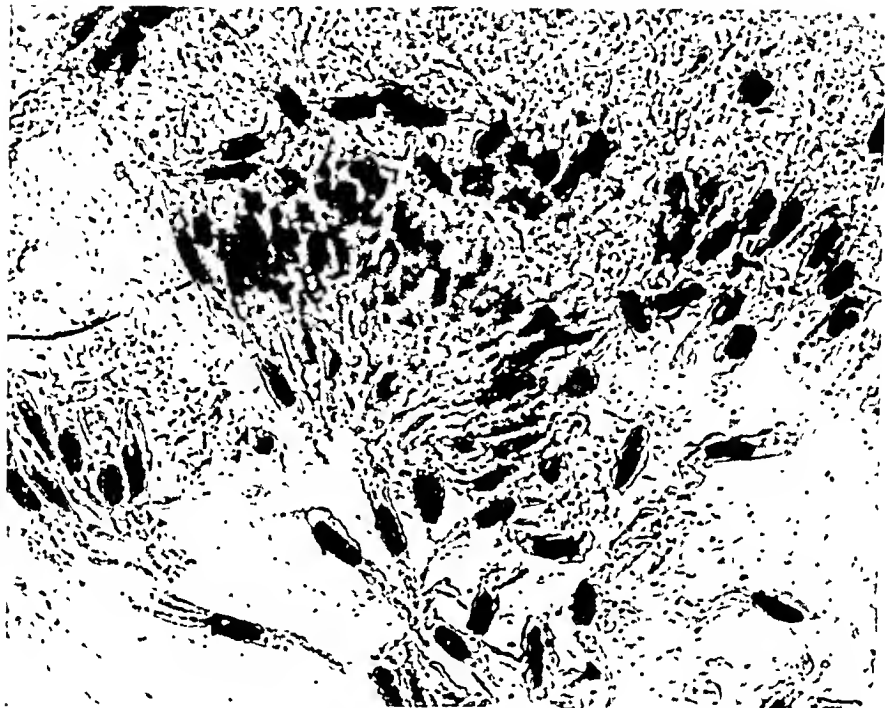


FIG. 6. SMEAR OF GASTRIC MUCUS—LARGE RANK OR PALISADE OF COLUMNAR CELLS BREAKING DOWN TO FORM A DISORGANIZED CLUMP OF INDIVIDUAL CELLS
Specimen—# 160.6
Stimulus—Water saturated with ether
Opacity—Opaque
Consistency—Viscous
Stain—Wright's
Magnification—675 x

TABLE 3

Contingency correlation: opacity and columnar cell content of specimens of non-acid gastric pouch mucus (all stimuli)

		COLUMNAR CELL CONTENT		TOTALS
		Few cells*	Many cells	
Opacity	Opaque	35 17.2%	88 43.1%	123 60.3%
	Non-Opaque†	53 26.0%	28 13.7%	81 39.7%
Totals		88 43.2%	116 56.8%	204 100%
$\chi^2 = 27.4$		n = 1	P < 0.001	

* Few cells = none or a small number of single cells per field.

† Non-Opaque = transparent or translucent.

respectively. By this statistical device, table 3 reveals that 65.4 per cent (53 in 81) of the non-opaque specimens contain few or no cells, and that 72 per cent of opaque specimens (88 in 123) are in the "many cells" category. χ^2 for this

correlation is 27.4 and n equals 1. For these values, P is well below the 0.1 per cent level, and it follows that there is a close association between opacity and high cell content on one hand and between transparency and absence of cells on the other. A similar analysis of the association of cell content with consistency (table 4) reveals further information of interest. A high viscosity is more likely to be associated with the presence of cells than with their absence; 61 per cent (116 in 190) for the former as against 39 per cent (74 in 190) for the latter. Distinctly fluid specimens, however, contain large numbers of cells much less frequently (12 specimens in 51, or 24 per cent). Hence, it appears that the presence of many cells augments the chance of occurrence of a high

TABLE 4

Contingency correlation: consistency and columnar cell content of specimens of non-acid gastric pouch mucus (all stimuli)

		COLUMNAR CELL CONTENT		TOTALS
		Few cells*	Many cells	
Consistency	Viscous	74 25.4%	116 39.9%	190 65.3%
	Fluid	39 13.4%	12 4.1%	51 17.5%
	Mixed	22 7.6%	28 9.6%	50 17.2%
Totals		135 46.4%	156 53.6%	291 100%

$$\chi^2 = 23.0$$

$$n = 2$$

$$P < 0.001$$

* Few cells = none or a small number of single cells per field.

viscosity, but a jelly-like consistency may characterize a specimen of relatively pure (cell-free) mucus as well. Nevertheless, since $P < 0.1$ per cent ($\chi^2 = 23.0$ and $n = 2$), the statistical significance of this correlation is amply established.

In the course of the routine examination of the Wright's-stained smears, it was noted that cells other than typical columnar epithelium were frequently present. Identification of these cells was impossible, however, because of the dense layer of mucus, and the destructive action of Wright's stain which was frequently encountered. The presence of nuclear residues from disrupted mucous cells complicated the problem still further. Metachromatic staining with toluidine blue overcame these difficulties to a great extent, and revealed leucocytes as well as other round or oval cells which may be goblet or neck chief cells. The details of the systematic study of such smears will be reported on later.

DISCUSSION

The foregoing observations make it evident that native gastric mucus, secreted in the absence of obvious acid secretion, may vary in consistency over an extremely wide range—up to that of a moderately stiff jelly. The term “consistency” is used advisedly. Words like viscosity, cohesiveness, adhesiveness, and tenacity represent essentially quantitative properties, and the present state of knowledge on the mucus problem does not yet warrant such physico-chemical measurements. The trichotomous classification of consistency employed herein—fluid, viscous, and mixed—has proven adequate for the purposes of this investigation; quantitative investigation of the more definitive properties may reveal significant relations between the physico-chemical and physiological characteristics of the secretion when more is known about the latter.

The color of the mucus specimens may be white to grey, yellow to tan, pink to red—or else colorless. The pink to red coloration indicates the presence of fresh blood in the specimen. A yellow tint also has been traced on occasion to the presence of minute amounts of blood, but not invariably so. A whitish or grey appearance of the secretion is a consequence of the particulate matter held in suspension. Specimens of jelly-like mucus which are entirely transparent and colorless are rarely obtained, but specimens which are colorless and translucent occur with considerable frequency. However, smears prepared from opaque, viscous specimens frequently reveal many small cell-free areas, resulting from a highly irregular distribution of the desquamated cells. Furthermore, gastroscopic observation of non-irritated mucosa, in dogs and in human beings, generally shows a glistening layer of transparent mucus covering the glandular epithelium; areas of opaque mucus are usually isolated and abnormal. Hence, the *pure* secretion is probably colorless, transparent, and homogeneous—even when its viscosity and tenacity are considerable.

In view of the heterogeneous character of all but the wholly transparent specimens, a quantitative determination of turbidity and cell content would have had but slight additional value in this investigation—in spite of its obvious value for statistical purposes in general. Violent stirring or shaking of the specimen to achieve homogeneity disrupts the cells and therefore could not be used. The destructive action of the staining procedure with Wright's stain on the intact columnar cells also contributed to the quantitative uncertainties of this investigation. In spite of these difficulties, the results of the χ^2 analysis unequivocally support the view that the content of columnar cells, intact and disrupted, is the major cause of the opacity. Coagulated mucin may also be a contributory factor, but it is less significant than the cell content. This interdependence of the appearance of a mucus specimen and its cell content was commented on by Mahlo (24), but he cited no evidence to indicate that the cells were chiefly the columnar cells rather than leucocytes. Our own results

in this regard, as indicated in our first preliminary report (17), have since been confirmed by Grant (10).

It has been found that, in general, the frequency of occurrence of viscous, jelly-like mucus is significantly correlated with the incidence of desquamated columnar cells. This observation is consistent with either of two hypotheses. 1—It may be postulated that we are dealing with two distinctly different types of secretion, both of which are cell-free:—one, a fluid material which is chiefly *mucoïd secretion* from the cuboidal cells; the other, a jelly-like material which is *true mucus* from the columnar cells. According to this hypothesis, the neck chief cells constitute a distinct type of exocrine gland, the product of which is the “mucoïd” or “dilution” secretion reported by previous investigators. 2—The alternative hypothesis presumes that there is only one type of secretion, and it also is free of cells; this is the true mucus which is elaborated by the surface epithelial cells and possibly also the neck chief cells. The consistency of this secretion may vary from that of a fluid to that of a jelly, depending upon variations in the physico-chemical characteristics of the mucus, which in turn are affected by the intensity of stimulation. Among these characteristics are included the concentration of the mucin, its intra-molecular arrangement, its degree of hydration, and its physico-chemical environment—especially the pH and other ionic concentrations. According to this second interpretation, however, the cuboidal cells are precursors of the columnar cells, possibly even immature mucus-secreting cells. Both hypotheses presume that the columnar cells suspended in the mucus, as it is usually collected, result from a secondary process involving the loosening of the inter-cellular cement substance. This also is a consequence of the action of the stimulus, but it is independent of the process of gland stimulation *per se*. As yet there is no positive evidence to support either postulation in favor of the other, but in both cases the correlation of consistency and columnar cell content of the specimens arises from the premise that the extent of desquamation and the proportion of jelly-like mucus both increase as the intensity of stimulation is increased.

Concerning the various stimuli which were employed in this investigation, it seems that the greater the irritant action of the agent, the greater is its effect as a stimulus to the secretion of jelly-like mucus. Goodman and Gilman (9) define skin and mucosal irritants as “drugs which act locally to produce inflammation”; they “can best be described as agents which injure protoplasm”, although mild irritation may induce only a localized vasodilation, without extravasation or desquamation. No attempt was made to quantitize the degree of inflammation which might be attributed to each of the stimuli here employed; erythrocytes and leucocytes were commonly observed in the smears, but their incidence was not evaluated. The occurrence of desquamated surface epithelial cells was evaluated, however, and was found to be correlated with the occur-

rence of jelly-like mucus. Based on the statements of Goodman and Gilman, this may be accepted as evidence in support of the correlation of irritant and mucus stimulating powers of the various agents. It is entirely consistent with this association of the two latter functions to interpret "spontaneous" mucus secretion as resulting from an extremely mild mechanical irritation—by the contractions of the gastric musculature and the gentle rubbing of mucosal folds upon each other. Evidence in support of this has been adduced by Hollander and Cowgill (16) and Hollander and Stein (18). Such stimulation might be expected to induce a mild reddening, probably no greater than the "healthy red" seen gastroscopically, as well as a low rate of mucus secretion. The mucosal massage employed in the present investigation probably induces about the same amount of "irritant" action as obtains in "spontaneous" secretion. Isotonic saline, on the contrary, possesses none of this irritant power but actually reduces the extent of mechanical irritation by reason of its lubricating action. It is interesting that distilled water may be slightly more stimulating to the mucus cells than the gentle rubbing employed in these experiments. Three-fold hypertonic NaCl, 50 per cent alcohol, and water saturated with ether, have a somewhat greater action than water alone; but the differences among these three agents are so slight as to make their order numbers, relative to each other, uncertain. Several experiments not included in the present data, demonstrate that the power to stimulate the output of jelly-like mucus increases with increasing concentration of the irritant. Clove oil in 5 per cent emulsion appears to be the greatest stimulus of all those investigated; as an irritant, however, even its action is relatively mild, for few of the specimens obtained by means of it give evidence of admixture with blood.

The protective function of mucus secretion in the stomach has long been recognized. Even Pavlov (25)—citing the work of Savriev on the application to the gastric mucosa of absolute alcohol, 0.2 per cent mercuric chloride solution, 10 per cent silver nitrate solution, and "a strong emulsion of oil of mustard"—indicated his belief that a copious flow of mucus in such experiments does not reflect "a serious pathological condition, an acute mucous catarrh", but only a normal physiological reaction to an irritant, which "dilutes the noxious substance, or forms chemical combinations with it, and expels it at the same time from the stomach wall. The surface epithelium thus wards off the danger which threatens the more important elements of the mucous membrane beneath." The results of the present investigation demonstrate that this protective activity involves two distinct processes: 1—the elaboration of a specific secretion, even under conditions of extremely mild irritation, and 2—a secondary process of desquamation under the impact of stronger stimulation. Evidently, the latter process is auxiliary to the former, and if simple mucus secretion is not sufficient to ward off the effect of a chemical irritant, then the

mucous cells themselves are shed, with the result that the destructive agent is carried away from contact with the more delicate glandular epithelium lying beneath. By what mechanism the inter-cellular cement substance becomes loosened under these conditions is still a mystery—all the more so since it does not occur uniformly, as evidenced by the presence of some intact palisades of columnar cells. It may be thought that exfoliation is a reflection only of repeated insult to the gastric mucosa, and therefore essentially pathological. That this is not so is shown conclusively by our observation that this phenomenon occurred in the first experiment performed with each dog, following the operation for preparation of its gastric pouch. Hence, the desquamation must be considered a normal physiological response to mild irritation, rather than a pathological reaction to repeated insult. This is also the view of B. B. Vincent Lyon (23), based on his study of smears taken at autopsy from the stomach of a patient with tuberculous gastritis and from the vomitus of a man suffering with an acute attack of food poisoning. Lyon's photomicrographs of smears of gastric mucus *per se*, revealed typical ranks of exfoliated columnar epithelium. A similar conclusion was reached by Grant (10), on the basis of her animal experiments, although her reports contain no indication of the frequency of occurrence of such intact ranks. Bockus (3) also has reported palisades of surface epithelial cells, embedded in a field of mucus from a case of achylia gastrica which did not respond to "gastritis therapy", but he drew no inference regarding their significance.

The term *mucous barrier* is coming into general use in connection with the protective function of mucus in the digestive tract, but especially in relation to the action of exogenous carcinogens on the gastric mucosa (20). In the light of the results of the present investigation it must now be recognized that this barrier consists not only of the layer of mucus which adheres to the surface of the mucosa, but also of the underlying mucous epithelial cells which can be thrown off by the stomach in order to carry away an offending agent.

SUMMARY AND CONCLUSIONS

In the foregoing investigation an attempt has been made to evaluate the relative frequency of occurrence of a number of characteristics of gastric mucus, and to study possible causal relations among these variables. The secretion was collected under the influence of six chemical mucosal stimuli; "spontaneously" secreted mucus and that obtained after rubbing of the mucosa were also studied. All the samples of mucus were obtained from dogs' Heidenhain pouches, under such conditions that they contained no obvious parietal secretion. *In toto*, around 500 specimens were examined. The results are summarized as follows:

1. Mucus may be either fluid or jelly-like or of any intermediate consistency—irrespective of stimulus.

2. Specimens of mucus may be transparent, completely opaque, or translucent.

3. Mucus collected under the conditions of these experiments may contain (a) neither cells, cell residues, nor even detritus; (b) much detritus, but no intact cells; or (c) large numbers of columnar cells—singly, in ranks, and in clumps. Erythrocytes may also be present occasionally; leucocytes occur more commonly.

4. Increasing viscosity, opacity, and columnar cell content are correlated with each other statistically. These three factors apparently correlate directly with the irritating powers of the stimulus as well.

5. The color of each specimen was recorded, but these data were not evaluated by statistical analysis.

6. From the above observations it may be inferred that pure mucus, as it is secreted, is (a) colorless, (b) transparent, (c) of variable consistency, and (d) free of suspended material. Opacity of a specimen as collected is the result of suspended material, chiefly desquamated columnar cells.

7. Two alternative hypotheses are offered to explain the variations in viscosity of the mucus collected in these experiments. One of these presumes that the neck chief cells and the columnar cells are distinct exocrine glands, giving rise to mucoid and mucus secretions respectively. The other hypothesizes that the cuboidal cells are precursors of the columnar cells, and that mucus—irrespective of its viscosity—may be elaborated by both of them.

8. The chief function of mucus secretion in the digestive tract is to protect the underlying glandular epithelium against various forms of irritation. This function entails two processes which probably are independent: exocrine secretion *per se* and desquamation of the surface epithelium. Because of the auxiliary protective device afforded by this exfoliation, the concept of a protective “mucus barrier” in the stomach has been redefined to include both of these processes.

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ISOLATED HODGKIN'S DISEASE OF THE STOMACH

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INTRODUCTION

Alimentary tract invasion by Hodgkin's disease is rare; solitary gastric involvement is exceedingly unusual. Hodgkin (1) gave his original description of the entity in 1832. Fifty-one descriptive synonyms (2), arising from difficulty in histological interpretation, make a survey of the literature difficult. Schlagenhauser (3), in 1913, probably reported the first instance of isolated gastric Hodgkin's disease. Of the comparatively few reported cases of Hodgkin's involving the stomach, most instances in the literature are examples of gastric invasion associated with the disease elsewhere. Illustrative, Hayden and Apfelbach (4), reviewing twenty-six cases of gastrointestinal Hodgkin's disease found only three instances of the involvement limited to the stomach.

When Singer (5) in 1931 correctly emphasized the curative possibilities in isolated gastric Hodgkin's disease his search of the literature disclosed six surgically managed cases. These included the cases of Steindl (6), Neuber (7), Von Redwitz (8), Froboese (9) and Vasiliu (10); surgical survival established their authenticity. Kan's (11) case and that of Singer's report died in the immediate postoperative period; autopsy confirmed gastric limitation of the disease.

In 1935 Comando (12) reported a five year surgical survival, Imai (13), a two year surgical result. Madding (14), in 1938, reported six operable correctable gastric lesions, there were two survivals exceeding six years, one eight years. Avent (15), in 1939, had a case expiring in the immediate postoperative period; Thune (16), that same year, reported two cases. The most recent report was that of Luxardo (17).

Clinically, the manifestations of the entity are indistinguishable from those of gastric ulcer or neoplasia which it simulates morphologically. Occasionally, there is a palpable mass. Weight variation is at extremes, maintenance to a seventy pound loss characterized the Mayo (14) report. Extremes in gastric analysis are recorded; achlorhydria is comparatively frequent.

Neither Pel-Ebstein fever, adenopathy nor the hematological findings, considered specific of Hodgkin's disease, should be considered a part of the picture of isolated gastric Hodgkin's disease.

Gastroscopy commented on by several observers (18, 19, 20) has been of no

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diagnostic aid. Our gastroscopic impression in Case D. V. was that of extensive infiltrating gastric carcinoma leaving an unexpectedly large lumen for such total involvement.

Gastrophotoscopic observation has not been previously commented upon. The findings in Case D. V. were interpreted to represent gastric carcinoma.

Kirklin (21) suggests that a soft diffuse lesion should be expected; in six cases he diagnosed five carcinoma and one an obstructive duodenal ulcer.

Jungman (19) in his discussion comments on the persistence of peristalsis though sluggish; he suggests a radiologic classification into three types:

- (1) Ulcerative, with multiple flat ulcerations.
- (2) Tumor-like masses in the prepyloric region with a narrow lumen.
- (3) Polyposis involving the entire stomach.

M. Teitlebaum (22), who suggested the diagnosis in Case A. C. based on his roentgenoscopic experiences in the study of Case D. V., comments upon the presence of sluggish peristalsis and the extensiveness of the roentgen defect not supported by a palpable mass.

Singer's (5) premise that isolated gastric Hodgkin's disease manifests itself sufficiently early to permit curative results by resection is supported by the reported survivals. When the surgical pathologist renders the diagnosis, the advisability of supplemental roentgen therapy (23) is to be considered.

The sparsity of reported instances of isolated gastric Hodgkin's disease, an estimated twenty cases properly so classified, indicates the rarity of the entity and justifies the report of these two cases. Case A. C. is perhaps the first to be diagnostic roentgenologically.

CASE REPORTS

Case I: Mrs. D. V. (Unit No. W-6074), admitted 6/10/44, a 55 year old woman complained of left hypochondrium pain of three years' duration. At Hutchinson Memorial Clinic, x-rays on 12/1/42 rendered a diagnosis of prepyloric lesser curvature ulcer. On 1/25/42 an acute abdomen led to exploratory at Charity Hospital with an operative diagnosis of acute phlegmonous gastritis with perforation. The defect was plicated; no biopsy was taken. She was asymptomatic during a four months' convalescent period.

Her pain was burning in character, localized to the left hypochondrium, intermittent, accentuated by food and relievable by alkali. Weight loss approximated thirty pounds. There was associated anorexia, progressive debility and intermittent retention emesis.

She was afebrile. There was no palpable abdominal mass. There was no adenopathy or splenomegaly.

Laboratory studies included normal gastric analysis, blood picture and serum proteins.

Chest roentgen study revealed only findings of inactive pulmonary tuberculosis.

Gastric roentgenology showed indentations on the anterolateral aspects of the greater curvature producing hemispherical filling defects in the cardiac region, there were extensive mucosal irregularities. Perigastric adhesions fixed the proximal third of the stomach. Peristalsis was demonstrable though sluggish.

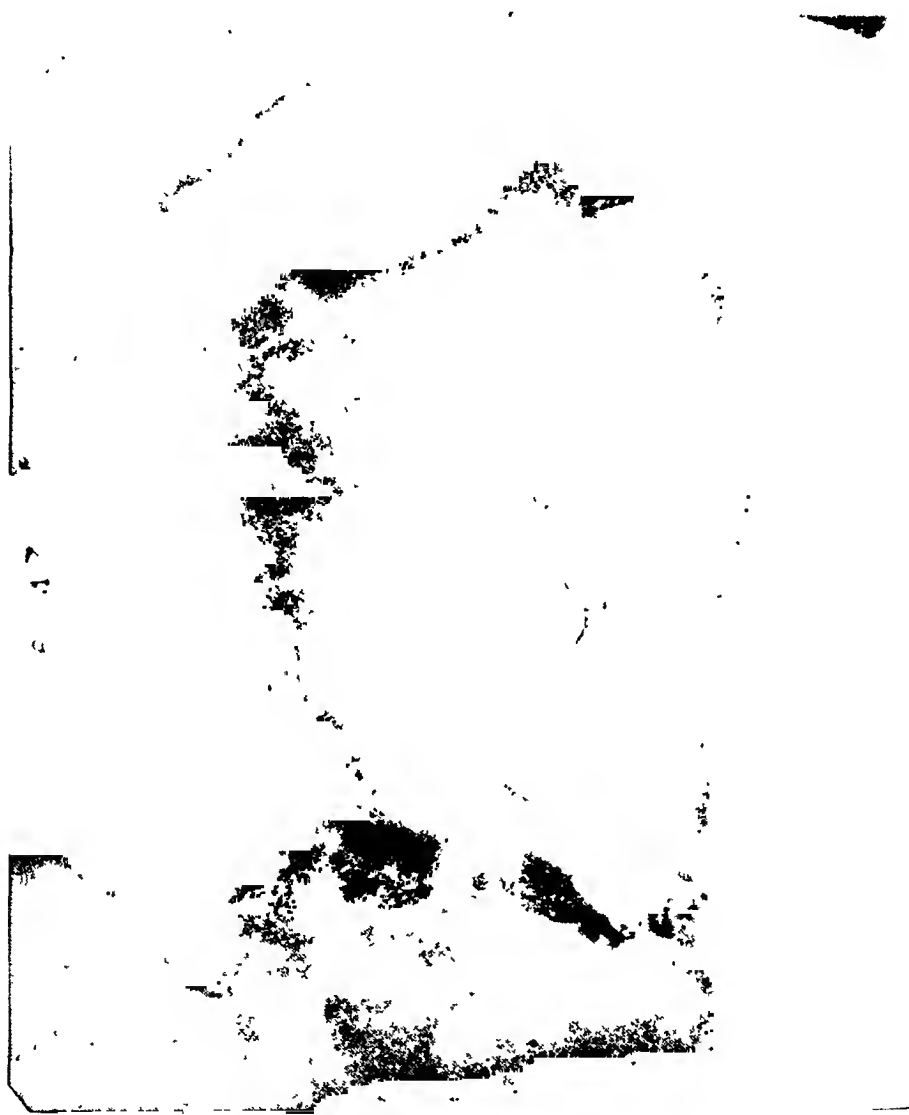


FIG. 1

Gastroscopy revealed in the proximal two thirds of the stomach a widespread polypoid hyperplasia with nodulations and ulceration, covered in part by a greyish exudate, seemingly held rigid, remarkably distensible and with an uninvolved pyloric segment.

Exploratory findings were interpreted as phlegmonous gastritis; the stomach could not be mobilized. A gastrostomy with intubation of the duodenum was done. Biopsy taken was reported anaplastic carcinoma.

Death on the twenty-eighth postoperative day was due to massive gastric hemorrhage.

Autopsy revealed extensive gastric Hodgkin's disease with involvement of the upper $\frac{2}{3}$ of the stomach and the perigastric nodes. The spleen and periaortic nodes



FIG 2

showed hyperplastic tuberculosis. The chest showed an inactive pulmonary tuberculosis. Complete autopsy revealed no evidence of other sites of Hodgkin's disease.

Case II: Mrs. A. C. (Unit No. X-2628) was admitted to the service of Dr. Emile Block 3/6/45. This 64 year old woman complained of localized epigastric pain of three years' duration, burning in character, often one to two hours postprandial and relievable by frequent small feedings. There was minimal dysphagia. The patient was a known hypertensive with manifestations of a low cardiovascular reserve.

Examination revealed only the findings of hypertensive cardiovascular disease. She was afebrile. There was no demonstrable adenopathy. There was no palpable abdominal mass.

Laboratory studies showed an achlorhydria and a mild normochromic, normocytic anemia with leukopenia. Serum Proteins approached edema level.

Chest films were normal.

The roentgenologic study revealed extensive greater curvature involvement of all but the cardiac segment. Sluggish peristalsis persisted. The findings, according to Dr. Teitlebaum, the roentgenologist, so closely simulated those encountered in Case D. V. that he suggested a diagnosis of lymphogranulomatosis.

At exploratory operation the gastric involvement permitted an extensive subtotal resection. There was no regional adenopathy and no evidence of other alimentary involvement.

The gross specimen showed a large fungating ulcerating mass producing a cup-like depression within the stomach at the cardiac extreme with a dipper-like handle of involvement extending down the greater curvature. The regional nodes were not involved. The findings were typically those of Hodgkin's disease. The patient is reported asymptomatic as of 1/30/46.

CONCLUSIONS

Isolated gastric Hodgkin's disease is rare. The operative curability of such lesions is proved. A clinical diagnosis cannot practically be made with our present knowledge of the disease but in its simulation to neoplastic disease it often manifests itself sufficiently early and significantly to indicate resection. Roentgen susceptibility probably improves the prognosis as a supplementary measure to resection.

Our two case reports supplement the limited literature and suggest roentgen findings indicative of the entity.

The Authors are indebted to Doctor Emile Block for permission to use the illustration and report of Case A. C.

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EDITORIALS

A NEW TREATMENT FOR SPRUE

In a recent number of *Science* (vol. 103, no. 2665) a note was made of the fact that the syndrome of vitamin M deficiency in the monkey resembles that of sprue in man. Since Day et al. (1945) showed that the avitaminosis in the monkey is quickly cured by the injection of a factor which greatly accelerates the growth of *Lactobacillus casei*, Darby, Jones and Johnson, of Vanderbilt University, decided to try the effect on sprue of the synthetic L. casei factor of Lederle (Augier, *Science*, 102, 227-228, 1945). They chose three patients with all the characteristics of sprue: glossitis, fatty diarrhea, weight loss, pigmentation of the skin, macrocytic anemia, slight leukopenia, poor intestinal absorption as shown by a flat oral glucose tolerance curve, as compared with a normal intravenous tolerance curve, a flat tolerance curve for vitamin A, a low serum carotene content and a characteristic gastrointestinal pattern on x-ray examination. Free hydrochloric acid was present in the gastric contents. The sternal marrow of two of the patients was typical of untreated sprue.

These patients received daily intramuscular injections of 15 mg. of the synthetic L. casei factor, and all three recovered promptly. The tongue soon became normal, the weight rose, the diarrhea stopped and the blood showed a fine reticulocyte response.

This splendid reaction led the writers to suggest that the new synthetic factor is identical with or very similar to the substance in liver that cures sprue. Since the factor that relieves the macrocytic anemia of pregnancy, so common in East Indian women, is closely related to vitamin M, the L. casei factor should be tried in the treatment of that form of anemia. Spies et al. have found it effective in the treatment of macrocytic anemias occurring in the United States.

W. C. A.

INTERFERENCE WITH BIOLOGICAL PROCESSES EFFECTED THROUGH THE USE OF DRUGS CLOSELY RESEMBLING ESSENTIAL METABOLITES

As every well-read physician knows today, the effectiveness of the sulfonamides is not dependent on any stimulation of the defense mechanisms of the body or on any simple germicidal action on bacteria.

As Welch (*Physiological Reviews* for October 1945) recently pointed out, early in the research that was done to throw light on the action of sulfanil-

amide it was discovered that there was some substance in certain culture media which was antagonistic to the antibacterial action of the new drug. When this substance was finally run down and identified, it was found to be *p*-amino-benzene-carboxylic acid. Sulfanilamide is para-amino-benzene-sulfonamide (the amide of sulfanilic acid) and the obvious conclusion was that the antagonistic substance, called "paba" for short, competed in the bacterial cell for the place in its metabolism that might otherwise be taken by sulfanilamide. Once in the cell the paba was of use in the metabolism of the bacterium while the closely related sulfanilamide was not.

A new name was coined for such substances; namely, *competitive inhibitors*. Such inhibitors are "mutually antagonistic components of a system in which the rôle of either the metabolite or the antimetabolite is reversibly and competitively interfered with by its antagonist, the relative amounts of the two substances in combination with the enzymic or other cellular components being dependent upon their relative affinities for them and upon their concentration-ratio."

Dr. Welch painted a picture of the natural substrate or metabolite as a key so notched and grooved as to fit perfectly into a lock of metabolic activity in the organism. The interfering substance is an imperfect key which, while grooved well enough to enter the lock, is not properly notched to open the door of metabolic activity. Unfortunately for the organism the presence of the defective key in the lock keeps the proper and needed one from entering.

As Welch went on to say, this conception promptly gave chemists a tremendously valuable directive in their research for new bacteriostatic drugs, and now it gives to all pharmacologists and physiologists an idea which should prove fruitful in finding antihormonal drugs and in understanding body chemistry.

Unfortunately, in spite of much research, not enough is yet known about the most profitable directions in which the chemist should search in order to produce antagonistic keys to fit certain locks. Many complicating factors also enter into the problem of securing a useful drug for a certain purpose. But certain basic principles are emerging from the study, and it does not seem likely that man would have stumbled on the only bacteriostatic substances available. Surely when he knows the whys and hows he will be able to synthesize his way straight to many drugs much better than the sulfonamides.

Anyone who is interested in this research will find Dr. Welch's article most thought producing. Another rich source of information is Selman A. Waksman's 350 page book on "Microbial antagonisms and antibiotic substances," published by the Oxford University Press in 1945. It contains a bibliography of 1,016 references.

W. C. A.

COMMENTS

Anti-ulcer (anthelone) products in the treatment of peptic ulcer

Since October, 1944, Swiss medical journals have published six articles discussing three "new" products prepared by a Swiss pharmaceutical firm for the treatment of "peptic" ulcer.

The three Swiss products are prepared from the mucosa of the hog's stomach and duodenum. One product contains extracts from the stomach of the hog (70%) and from the small intestine (30%). The second product comprises these same extracts in reverse ratio. These are administered parenterally. The third preparation, a tablet, administered orally,¹ "is of one kind only," and is for both gastric and duodenal ulcers.

An analysis of the six publications, which were brought to the attention of the writer by Lt. Col. S. G. Meyers, who was in charge of gastroenterology at the 17th General Hospital in Italy, gives the impression that, while the reports are encouraging, they are somewhat colored by enthusiasm. In aggregate, they deal with only 125 cases of peptic ulcer and also include 17 non-ulcer cases. The Swiss workers discuss the "immediate" result during or after therapy, but fail to compare their data with "control" parenterally-treated cases of other workers, or to present any "control" series of their own.

While several "relapses" are reported, the authors do not present convincing "follow-up" end-results of their treated cases. While they recommend periodic prophylactic treatment of individuals liable to ulcer by oral administration of the tablets, they do so without presenting experimental data or convincing clinical experiences to warrant their enthusiastic recommendation.²

The following salient points were made in the six publications dealing with the Swiss preparations:

Hemmeler (6) treated some 20 persons, eight of whom received no supplementary treatment. All reacted favorably, the ulcer being cured both

¹Rivers (1), in 1925, was first to prescribe orally an extract of duodenal mucosa and submucosa, reporting encouraging results in detail in eight cases out of his experience with 50 patients. He expressed the hope that when the specific factors of duodenal tissues are identified and isolated "there will undoubtedly be made available a substance of great usefulness in the treatment and in the prevention of recurrences of peptic ulcer". In 1937, Stalker, Bollman and Mann (2), reported "some benefit" from the use of 10 gms. of duodenal extract daily in cinchophen fed dogs. More recently (1945), Morrison (3) reported that dogs fail to develop cinchophen ulcers if fed each day (in addition to yellow cinchophen) one-half pound of hog stomach and duodenal preparation.

²Ivy (4) in the Sept. 1945 issue of the Federation Proceedings, presented preliminary data on the oral effectiveness of crude extracts of the upper intestinal mucosa in Mann-Williamson dogs. He states that the ulcer preventing agent is active orally but that "it is too soon to conclude that lasting protection will result from oral therapy!"

clinically and radiologically ("in one case the Haudek niche has not yet entirely disappeared"). "The fact that so far we have not encountered a failure is probably to be explained by the restricting of our observations. It is probable that very old or penetrating ulcers may be no longer capable of being favorably influenced by internal therapy and require surgical intervention." In the eight cases on which Hemmeler presents detailed data, the patients were not confined to bed or kept on a special diet. They received no medicaments other than the gastro-intestinal extracts. Hemmeler is careful to state that it is premature to conclude that this represents the "therapy of the future."

Schmassman (7) summarizes results in the treatment of fifty persons as follows: Symptoms disappear rapidly, often coincident with commencement of treatment. Fresh ulcer niches completely disappear in a minimum of three weeks, as disclosed by radiological examinations. Superacidity decreases in cases of gastric ulcer and gastritis, but acidity tends to increase in cases of duodenal ulcer. Diet can be relaxed, time spent in bed reduced, and all symptomatic therapy eliminated without adverse effects. Undesirable secondary effects are rare by proper application (deep intragluteal injection). Treatment may be given without danger to patients with bleeding ulcer. Chronic ulcer cases with relapses extending over a long period of years can be freed from symptoms, although severe alterations with cicatrization cannot be removed. Very large ulcers situated on the lesser curvature become much diminished in size, but disappear only by use of transduodenal feeding. Schmassman further states that, as anticipated, the treatment has no effect in cases requiring surgical intervention, and that, while some measure of prophylaxis appears to be attainable by oral administration of the tablets, the observations do not extend over a long enough period of time to permit conclusions as to effects on the tendency to relapse and on the basic constitutional predisposing factors.

In seven cases which Schmassman followed subsequent to the treatments, five observed recurrence of symptoms. Three of these stated that their symptoms again disappeared after taking the tablets, but reappeared to some extent in a few weeks after they ceased to take them. Two persons with chronic ulcer declared that, following treatment, though their symptoms returned from time to time, they were less hindered in their capacity to work, and on the whole, distinctly better than in previous years. In four cases (one an ulcer-carcinoma), surgical intervention became necessary after two to seven months.

Mamie (8) employed the Swiss preparations in 26 cases (11 gastric ulcer, 12 duodenal ulcer, 3 gastro-jejunal ulcer). He cites results so far obtained as showing that "the preparations have an extremely favorable effect on the evolution of all gastro-duodenal ulcer, affording rapid amelioration and even

the complete disappearance of the subjective symptoms." He states that, radiologically, gastric ulcers generally vanish without trace, though cicatrization remains. Cases presented by Mamie were also ambulant and on full diet. He stresses the fact, that because relapses are frequent, "the treatment of ulcer does not of itself suffice to protect the patient against a new attack," and advocates repeated courses of the Swiss preparations in tablet form as a prophylactic measure, especially during spring and autumn when relapses most frequently occur.

Berther (9), in reporting his observations on ten cases of gastric ulcer and ten cases of duodenal ulcer, noted that "rapid subjective attainment of freedom from symptoms has been striking" and "that freedom from pain has been observed within ten to fourteen days." He further states that "the rapid attainment of freedom from pain and the simplicity of the therapy enable the general practitioner to treat his ulcer patients as ambulant cases." Berther also stresses prophylactic treatment for some time by administration of the tablets.

Roulet's report (10) deals with histamine-produced ulcers in the guinea-pig, originally described by Merkel (11) in 1942 and corroborated by Roulet and Frubiger (12). Some 40 to 50 days after commencement of the experiment, finding a gastric ulcer, Roulet administered 0.1 gm. of the powder contained in the Swiss tablets by a stomach tube and gave daily sub-cutaneous injections of 1 cc. of the mucosa extracts for 21 days. He states that he noted healed or healing ulcers in ten guinea-pigs. Attempted prophylactic treatments in these animals with the Swiss preparations during three weeks failed to protect them against histamine ulcers.

Keiser (13) reports on 38 cases treated with the above preparations (14 gastric ulcer, 16 duodenal ulcer, "3 cases following duodenal ulcer, 1 of *Ulcus Jejuni Pepticum*, 1 following gastrectomy, 2 of hyperacidity, 1 of sub-acid gastritis). All were treated as ambulant cases, without special diet, and with supplementary rations given to only a few patients. Says Keiser: "Twenty-nine cases showed an improvement and six cases were cured". (By "cured," he means cases where a symptom-free interval follows and the ulcer is no longer detectable radiologically. By "improved", he means free from symptoms, but not checked radiologically.) Nine relapses were encountered, of which three had been classified as "cured." Keiser also advocates periodic prophylactic treatment.

The Swiss company does not present any report of independent investigations which led to the production of these preparations. It refers to Entero-gastrone and Urogastrone, with regard to their action on gastric secretion and motility as well as to their effect on Mann-Williamson ulcers (thus referring to Anthelone), and apparently base the products on the work of Ivy and his

colleagues (4, 14, 15, 16), Necheles et al. (17), Friedman et al. (18, 19), Beaver et al. (20) and Sandweiss and his associates (21-24). If the Swiss products do in fact, as it appears now, deal with the anti-ulcer factor first described by the American investigators, it would appear wise to follow the nomenclature used by the American groups, in order to avoid confusion.

David J. Sandweiss

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3. Bredgade

Copenhagen, Denmark No. 1, 1945

Dr. H. Necheles

Michael Reese Hospital

Chicago 16,

Ill., U.S.A.

My dear Dr. Necheles,

How funny that you received my letter after five years' delay. Much has happened since I wrote it, but fortunately my family and I got safely through

all the troubles. Now we are free again and are very grateful to your nation for all that you have done. We are glad to have your brave boys here in Denmark and they seem to be glad to stay here. Your language is heard in our streets just as frequently as our own. I remember the discussions I had with colleagues in U. S. A. just before the war. I foretold them the events just as they occurred: The Nazi aggression, the occupation and the new world war. I foretold that U. S. A. would once more have to send her youth to the European battlefields and once again fight for freedom and humanity shoulder to shoulder with us. However, they doubted that U. S. would once more send her boys into death in Europe—but I was right. History was repeated!

In the meantime we have had the "pleasure" of a very intimate acquaintance with the Nazi system. It gives a kind of experience although not exactly a pleasant one. We have had them here for five years. I wonder if you can imagine what that means: nights and days of anxiety, cruelty and danger. Lots of our young men were either brutally shot down or tortured to death in German prisons or concentration camps. In spite of the overwhelming power, however, we took up the battle and organized the Resistance Movement. For the first time the Nazi devils had to learn what it meant to try to suppress an intelligent, brave and free nation. The sabotage hindered their movements, troop trains were destroyed, factories which were forced to work for the "Wehrmacht" were blown up, food supplies were delayed. At last they were completely confused, and their cruelty grew from day to day. We never gave up. We never surrendered. And we won!

Materially we have suffered only little. We have had food enough and our production apparatus is almost intact. Of course we have been missing many things, and mentally we have of course suffered much.

Now we strive to return to peaceful conditions, which seems to be difficult enough. We trust you in U. S. A. and hope that you may settle the affairs satisfactorily so that we may look forward to a peaceful future.

In spite of the Nazi occupation we tried to do our work as usual, and scientific work has been my consolation. I have published some articles on gastroscopy in the *Acta Med. Scandinavica* and in the Swiss journal "*Gastroenterologia*," but as I could not write in English, I wrote in "Austrian" or French. I have written about the gastrosopic findings in achylia and the postoperative gastritis, which confirms the investigations of Dr. Schindler. I am preparing an article along the same line together with one of my surgical colleagues.

Moreover very extensive investigations into the biological effects of liver extracts with special reference to the gastric-stimulating principle have been published by one of my pupils.

After years of isolation I am glad to reestablish communication with you and my many other good friends in U. S. A., and I hope some day to be able to

cross the ocean again and meet you personally for I do not think that you should feel any attraction in coming over here to the ruins of civilization, although I should be glad to have you.

Unfortunately I do not think that conditions in much of Europe will be tolerable for years.

Yesterday we had the first election to parliament after the war. Maybe it will interest you to hear that our greatest party, the socialist, was *defeated*. They lost a lot of votes to the communists, who previously had a very feeble representation in our parliament. Now they gained a good deal, but not as much as could be expected from the elections in other European countries. The conservative parties, especially the agricultural one, together won the majority. This is very interesting, for now you will see the surprising fact, that we will here in Denmark have a *conservative government for the first time in 15 years*. The communists could not get a foothold in this country. And our labour party (the socialists) has lost its majority. On the background of what is happening in the political arenas of the world this is very noticeable and causes a little optimism as to the future.

Sincerely yours,

Dr. Tage Christiansen

HEALTH IN CHINA

The January, 1946, number of the "National Reconstruction Journal" of the China Institute¹ is fascinating reading for any person interested in China or in geographic medicine. In a number of papers, qualified Chinese doctors and scientists review and take stock of the medical situation in China after eighty years of devastating war, and lay plans for the reconstruction of hygiene, medicine and science in postwar China.

This number of the Journal makes sad reading when we see how tuberculosis is ravaging China, with a death rate eight times that of the United States, and prevailing among students, teachers, professional groups and civil service employees. The deaths from tuberculosis during this war were far greater than the number of war casualties. Other infections, such as malaria, dysentery, kala azar and schistosomiasis are devastating. One reason for these conditions is malnutrition, which is undoubtedly one of the most important factors. Most Chinese, irrespective of their social status, have existed for more than a decade on diets insufficient in quantity and in quality. Particularly noteworthy has been an acute shortage of protein foods like eggs, fish, meat, etc. which are essential for building up health and resistance.

H. NECHLES

¹ Vol. 6: 3 (January) 1946, China Institute in America, New York City.

BOOK REVIEWS

RADIOLOGIC EXAMINATION OF THE SMALL INTESTINE. *By Ross Golden.* Lippincott, Philadelphia. 1945. 239 pp. \$6.00.

This well-written, well-illustrated and attractive book will be welcomed by roentgenologists and internists. It contains much information which is not easy to gather together or to find in one place.

In view of the fact that the small intestine is the main organ of digestion it is unfortunate that gastroenterologists know so little about it in health or disease, and so seldom try to learn anything about it in the individual patient. A small bowel study with the roentgen ray takes time and care, and hence the busy roentgenologist dreads the making of more than a few such examinations in any one day. He is right also when he protests that rarely do such studies reveal anything of diagnostic value. The answer is that they should be made only when a wise clinician feels that they should be made to exclude intermittent obstruction or the presence of regional enteritis or a jejunal hemangioma or a spruelike picture.

The book should be on the shelf of every gastroenterologist. There are chapters on the small bowel of the infant, on the use of the Miller-Abbott tube, on ileus, disorders of nutrition, diseases of the mesentery, allergy, and the effects of certain drugs on the gut.

DR. W. C. RÖNTGEN. *By Otto Glasser.* Charles C Thomas, Publisher, Springfield, Illinois, 1945. 169 pp. \$4.50.

Dr. Glasser, with his tremendous and intimate knowledge of Röntgen and his great discovery, has written a delightful book which gives a description of the thoughts and experiments which gave the world the first knowledge of the roentgen rays. Contrary to the usual statement, the discovery was not so much the result of accident as of a definite and well-planned study of the cathode rays. It was while running a tube well covered with black paper that Röntgen saw his little fluorescent screen light up where it lay on a near-by bench. He knew instantly that here were signs of a new type of radiation because the cathode rays could not pass through more than a few inches of air. Soon afterward, while studying the penetration of various substances by the rays, he was startled to see his fingers with the bones showing up. Interestingly, just six years before, an accidentally produced roentgenogram was found by Goodspeed in Philadelphia, but its method of production couldn't be understood or explained and hence it was thrown aside.

It is interesting to note how quickly after December, 1895, the new rays were put to work. For instance, arteriograms were promptly made with the help of opaque salts injected into arteries. Within six months it was discovered that the rays were injurious to the skin, but not before a number of men were seriously injured. Röntgen had sense enough almost from the start to protect himself with lead foil.

In this book, one finds helpful translations of Röntgen's first three papers on the new rays.

WHAT PEOPLE ARE—A STUDY OF NORMAL YOUNG. *By Clark W. Heath.* Harvard University Press, Cambridge, Mass., 1945. 141 pp. \$2.00.

This is a valuable little book which might well be read by every physician since it deals with the problems of what is normal in the physique and physiology and mental and temperamental make-up of young American men. One serious fault of medicine today is that physicians, never having been given much information as to what is the normal range of the many figures for bodily functions, spend much of their time treating such perfectly harmless variations from the norm as a basal metabolic rate of -12 per cent or a blood pressure of 100 mm. of mercury. In a group of 182 apparently normal students the basal metabolic rate ranged from -27 to $+26$ per cent and the systolic blood pressure (recumbent) from 98 to 146 mm.

The men were classified as to traits, first into groups of "excellent," "normal," and "difficult" and then under such headings as well-integrated, vital effect, political, bland effect, friendly, pragmatic, humanistic, practical organizing, shy, self-driving, ideational, inarticulate, inhibited, verbalistic, cultural, just-so, sensitive effect, unstable autonomic functions, self-conscious and introspective mood fluctuations, lack of purpose and values, asocial, incompletely integrated, and creative and intuitive. As one would expect, a number of traits tend to group themselves in certain individuals. Among these combinations, a common one is that of friendly, humanistic and vital effect, while at the other end of the scale one finds combinations of incompletely integrated, shy self-conscious and introspective, and asocial.

Under physical make-up were listed masculine component, strong, moderate, weak or very weak. In addition there were disproportions between different parts of the body. Interestingly, the groups with the higher numbers of disproportions were more subject to disorders that caused them to be sent to a psychiatrist for advice. Here we have evidence to show that a healthy mind is a bit more likely to be found in a shapely body than in a misshapen one.

It is to be hoped that many more studies of this type will soon be carried out and widely published.

THE ART AND SCIENCE OF NUTRITION. *By Estelle E. Hawley, Ph. D. and Grace Carden, B. S.* St. Louis, C. V. Mosby Co., 1944. 668 pp. \$3.75.

Misses Hawley and Carden have prepared a readable and well-illustrated textbook suitable for dietitians and nurses. In many places the information is presented graphically with the help of the sort of drawing one finds often on the walls of museums of teaching institutions.

About a third of the book is filled with menus and instruction for running a school of dietetics. There are many fine colored illustrations. The teacher of dietetics will find much helpful information in this book. It is distinctive.

THE DIAGNOSIS AND TREATMENT OF ACUTE MEDICAL DISORDERS. *By Francis D. Murphy.* F. A. Davis Company, Philadelphia. 1945. 509 pp. \$6.00.

This book deals with those acute medical diseases which call for prompt diagnosis and treatment. Every medical emergency of any practical significance is discussed briefly but well.

The types of cases described are those commonly seen in the emergency wards of a big hospital. They require special training of the consultant if he is to recognize them promptly. Dr. Murphy describes not only the more commonly presenting aspects of these diseases but also the more puzzling ones. He appears to be particularly interested in the cardiovascular and renal conditions, the blood dyscrasias and the metabolic disturbances.

The surgeon will find much useful information not only in the chapters on the acute abdomen but also in those which deal with diseases of the lung and their tendency to simulate a surgical abdomen. The final chapters give advice as to the use of the drugs more commonly employed in these acute situations.

It is good to have all the many conditions that produce acute emergencies described in one book. There is many a clinician who is well trained to handle patients who come to the office with the chronic types of disease but unless he spends much time in the emergency wards he is not likely to be well fitted to handle the problems of diagnosis which come up there. He will not be ready to make a diagnosis when a patient comes in in coma or in such pain that he cannot give much of a history.

Vasilii Nicholaevich Boldyreff

On February 27, 1946, death came to Dr. William Nicholas Boldyreff, the well-known Russian physiologist. Dr. Boldyreff's name is a familiar one to those interested in gastro-intestinal physiology. His doctoral dissertation on "The periodic activity of the digestive organs in fasting" is an oft-quoted *classic* in which he accurately described for the first time the motility of the fasting stomach which later was shown to be associated with hunger. He is also noted for his observations on the rôle of enterogastric regurgitation in the control of gastric acidity.

Vasilii Nicholaevich (changed to William Nicholas upon coming to this country) Boldyreff was born on January 10, 1873, in Voronezh, Russia. After being graduated from the Imperial Military Medical Academy in St. Petersburg in 1898, he served for two years as a military surgeon in the Caucasus and for one year as a physician in a State Hospital.

The years 1901 to 1912 were spent at the Imperial Institute of Experimental Medicine in St. Petersburg first as a pupil and later as chief assistant to the renowned Ivan Pavlov. Then followed a three year tenure of the chair in pharmacology at the Imperial University of Kazan. When the First World War came he volunteered his services and was assigned to the Red Cross as a poison gas defense expert with the rank of Brigadier General. In this capacity he was sent to France and England, and he was there when the revolution broke out.

In the face of many hardships, he returned to Russia and in the fall of 1918 he moved his family across Siberia to Japan where he became guest lecturer in physiology at several of the universities including those at Kyoto and Tokyo.

Coming to the United States in 1922, Dr. Boldyreff lectured on experimental physiology for one year at Western Reserve University. From 1923 until his retirement five years ago he was director of the Pavlov Physiological Laboratory at the Battle Creek Sanitarium.

His many friends and acquaintances among American gastroenterologists will learn of his death with regret.

A. C. Ivy



Vasilii Nicholaevich Boldyreff

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MOUTH AND ESOPHAGUS

CLAGETT, O. T., MOERSCH, H. J. AND FISCHER, A. Esophagogastrostomy in the treatment of cardiospasm. Surg. Gyn. Obs., 81: 440 (Oct.) 1945.

Esophagogastrostomy is not intended as an initial procedure in the treatment of cardiospasm. The majority of patients who have cardiospasm obtain excellent results from dilatation of the cardia by means of the hydrostatic dilator. Approximately 70% of patients are completely relieved by one course of treatment. In 30% of cases, there is a tendency for the condition to recur. Recurrence may take place at any time from immediately after treatment to as much as 25 years thereafter. If the condition does recur, the majority of patients can be relieved by subsequent dilatation. In 2 to 5% of the cases, hydrostatic dilatation does not prove efficacious and surgical intervention is indicated.

The authors recently operated on 4 pa-

tients with cardiospasm of long standing, in whose cases dilatation of the cardia had failed to produce more than temporary relief. The operative procedure employed was esophagogastrostomy. Although in each case a very good functional result was obtained, the dilated esophagus did not appear to reduce appreciably in size following operation, an observation which has also been noted after esophageal dilatation.

FRANCIS D. MURPHY.

BORTONE, F. Esophageal diverticulum. Am. J. Surg., 69: 64 (Oct.) 1945.

Pharyngo-esophageal diverticulum arises just above the beginning of the esophagus, as a sac from the posterior aspect on the left side, and is made up of the mucous and sub-mucous layers of the pharynx. Resulting from mechanical pressure, they bulge through a transverse aperture forced between the pars obliqua and pars fundiformis of the cricopharyngeus muscle. Preopera-

tive fluoroscopy will establish the exact position in relation to the side of occupancy and the site of primary incision. Surgical excision is carried out in two stages, with an interval of 8-10 days between. Careful dissection and walling off of the mediastinum will prevent the serious complications of leakage and mediastinitis. Details of the surgical technique are adequately described and illustrated.

MICHAEL W. SHUTKIN.

STOMACH

FLETCHER, C. M. AND JONES, F. A. The risks of gastroscopy with the flexible gastroscope. *Brit. Med. J.*, 4421: 421 (Sept.) 1945.

Wolf and Schindler called their flexible gastroscope "entirely safe." They claimed there was no risk of lower oesophageal perforation. Accidents, however, have occasionally occurred. One death was due to hypopharyngeal perforation of the oesophagus. There were also 8 instances of gastric and one of jejunal perforation without fatality. A further non-fatal case of gastric perforation attributed to the use of the sponge-rubber tip has been reported. Since then, 3 additional cases of hypopharyngeal perforation with the flexible gastroscope have been reported, one of them fatal. The Hermon Taylor gastroscope was used in both fatal cases reported by the authors. The flexible part of the Hermon Taylor gastroscope is 2 mm. wider (i.e., 14 mm. wide) and is appreciably stiffer than the corresponding part of the original Wolf-Schindler instrument. It is possible that extra care is necessary for its passage into the oesophagus. The Hermon Taylor model gives a much better view of the stomach than can be obtained with the Wolf-Schindler instrument. In the two cases, hypopharyngeal perforation of the oesophagus has occurred. It is important that inexperienced gastroscopists should appreciate that caution is necessary in the passage of the flexible gastroscope.

H. NECHELES.

BOWEL

PALMER, W. L. AND RICKETTS, W. E. Chronic ulcerative colitis with generalized

peritonitis and recovery. Treatment with penicillin and sulfadiazine. *Arch. Surg.* 51: 102 (Sept.) 1945.

In 3 cases of chronic ulcerative colitis with manifestations of generalized peritonitis, recovery was attributed primarily to therapy with sulfonamide compounds and penicillin, although blood transfusions and other supportive measures were used. In 1 patient, two large abscesses were subsequently drained surgically. In another patient laparotomy 3 weeks later disclosed the loops of bowel bound together by the recent adhesions characteristic of peritonitis. In the third patient, the clinical picture was typical of peritonitis, but no operation was performed. In general, sulfonamide compounds tend to inhibit the growth of gram-negative organisms in the bowel and penicillin than of gram-positive organisms. The possibility of a synergistic action of the two drugs also exists.

FRANCIS D. MURPHY.

HAWE, P. The surgical aspect of intestinal amebiasis. *Surg. Gyn. Obs.*, 81: 387 (Oct.) 1945.

Intestinal amebiasis is of major surgical importance in endemic areas. With the return of the armed forces from the East, many cases must be expected in general practice. Clinical and radiological manifestations of the localized forms of intestinal amebiasis may be indistinguishable from those of surgical diseases, acute or chronic. It is usually possible to find *Endamoeba histolytica* in the stools; sigmoidoscopy may succeed when stool examination fails. Response to emetine is of diagnostic importance, but occasionally the condition is resistant to the drug and exploration or biopsy is required. The possible coexistence of amebiasis with other lesions must not be ignored. Clinical features of acute cecal amebiasis and acute appendicitis are similar; differential diagnosis may be difficult. In view of the risks of operation in cecal amebiasis, every effort must be made to obtain a clinical diagnosis.

Localized chronic amebic colitis and ulceration of the rectum may be mistaken for carcinoma or other surgical disease. Minor

anorectal conditions may result from unsuspected mild or chronic amebiasis. With few exceptions abdominal or rectal operations are contraindicated in patients with intestinal amebiasis; they are often followed by complications peculiar to this disease. If operation is necessary, or if amebiasis is discovered at operation, the sooner emetine is given the better. Appendicostomy and cecostomy have no place in treatment.

FRANCIS D. MURPHY.

DIXON, C. F. AND BENSON, R. E. Carcinoma of sigmoid and rectosigmoid involving urinary bladder. *Surgery*, 18: 191 (Aug.) 1945.

This is a review of the problems encountered in managing 64 cases of carcinoma of the sigmoid and rectosigmoid involving the urinary bladder. Slight involvement of the bladder by carcinoma of the sigmoid may exist without clinical evidence and be discovered only at operation. With extensive bladder involvement distressing urinary symptoms may develop. Bowel symptoms, however, usually over-shadow urinary symptoms.

Of the 64 patients treated by Dixon and Benson, 59 were males. The low incidence in females is probably due to anatomical differences in the pelvis. Involvement of the bladder is usually a late phenomenon and occurs after the tumor is large and has extended well beyond the bowel. The first step in bladder invasion is probably inflammatory attachment of the tumor to the bladder. If inflammatory reaction is marked, colostomy preliminary to resection may be considered, but the authors believe that preliminary resection is advisable if at all possible. Resection was done in 40 of these cases, with 7 operative deaths. In most of the patients who had resections, an end-to-end anastomosis was performed. In the remaining 22 cases, only palliative operations were done. Of the 40 patients subjected to resections, 20 were alive at the time of the report, 17 having survived for more than one year and 7 for more than 5 years.

HENRY TUMEN.

HOERR, S. O. Mortality factors in acute appendicitis. *Surgery*, 18: 305 (Sept.) 1945.

This is an analysis of the findings among 100 deaths in 2195 cases of acute appendicitis at the Peter Bent Brigham Hospital from 1913 to 1940. The average mortality during this period was 4.6%, with no tendency for improvement in this figure occurring during the recent years. This mortality figure is not widely different from that reported from other institutions. For the purposes of consideration, the cases are grouped as acute unruptured appendicitis, acute perforated appendicitis, and appendiceal abscess.

Eighty of the operative cases died as a result of progressing appendicitis or its complications. Of these 80 patients, 53 had acute perforated appendicitis, 14 had appendiceal abscess, and only 13 had acute unruptured appendicitis. These findings, and the fact that there were only 6 fatalities in patients operated within 30 hours after the onset, support the statement that delay in operation is a major factor in producing a fatal result. Another factor causing an unfavorable outcome is the use of cathartics, since 49 of the 80 patients had received cathartics. Of the patients who died, 15 had undrained residual abscesses at the time of death; these abscesses should be looked for in patients who are not improving after 2 weeks from the onset of the disease. Ten patients died from severe ileus or mechanical intestinal obstruction. It is possible that more energetic preventive measures, or reoperation, might have avoided some of these deaths.

The use of large doses of sulfonamides does not guarantee recovery of the patient, since 3 patients died despite what would be considered adequate amounts of these drugs. Statistics are presented which indicate that a slightly lower mortality results with the use of a McBurney incision, and with the use of a closure without drainage.

HENRY TUMEN.

KREMEN, A. J. Acute colonic obstruction secondary to carcinoma of the sigmoid colon with gangrene of an extensive segment of the large bowel. *Surgery*, 18: 335 (Sept.) 1945.

This is a report of the occurrence in a 43 year old man of acute obstruction of the colon, secondary to annular constricting napkin ring tumor of the sigmoid about 15 cm. around the peritoneal reflection. The distension of the colon was extreme, and had resulted in gangrene of the entire colon from the ileocecal valve to the mid portion of the descending colon. Because of the extent of the gangrene, it was necessary to do a colectomy. Approximately 7 weeks following this, an end-to-end intraperitoneal ileosigmoidostomy was performed. At the time of the report the patient was entirely well.

This case report emphasizes the extreme intraluminary tension which may develop in the colon in the presence of acute obstruction. This was sufficient to produce gangrene of the colon within a period of 9 hours from the time of the onset of the complete obstruction, without perforation developing in the cecum.

HENRY TÜMEN.

HENKIN, A. L. Postpartum intestinal obstruction due to adhesion bands. N. Y. State J. Med., 45: 1989 (Sept.) 1945.

A case is presented in which partial intestinal obstruction due to a congenital band occurred a few hours after delivery. The patient was considered to suffer from a chronically diseased appendix because of several attacks of right lower quadrant pain. About 4 hours after spontaneous delivery right, lower quadrant pain was complained of. There was general tenderness, and rebound tenderness on the right side. The temperature was 99.6° F; white blood count was 17,900. At operation the cecum was found to be rotated and partially constricted by a thick fibrous band. The appendix was retro-cecal; it was found to be normal on inspection, but pathologic section revealed leukocytic infiltration.

PHILIP LEVITSKY.

LUST, FRANZ J. Roentgenological diagnosis of benign tumors (single polyps) of the colon. Am. J. Roent. Radium Therapy, 54: 276 (Sept.) 1945.

The important clinical signs suggesting intestinal polyps are (1) bleeding from the rectum and (2) intestinal obstruction.

Bleeding is frequently the first symptom. Benign polyps are rarely large enough to produce complete occlusion. One should suspect a pedunculated polyp of the colon if the patient, in the absence of pain, experiences pain following laxatives or enemas. The best method for finding a polypoid growth of the colon (exclusive of the rectum) is by the barium enema and insufflation of air. Fluororoentgenography with localized compression is an important part of the examination in the differential diagnosis. Three cases are reported with roentgenologic illustrations demonstrating a polyp. The author stresses the importance of the study of the mucous membrane of the colon after evacuation.

MAURICE FELDMAN.

GRIFFIN, W. D., BARTRON, G. R. AND MEYER, K. A. Volvulus of the sigmoid colon. Report of twenty-five cases. Surg. Gyn. Obs., 81: 287 (Sept.) 1945.

Two main types of sigmoid volvulus are differentiated:

(1) *Acute*: (7 cases) occurring in younger age groups; characterized by short onset, equivocal history of constipation, early transient emesis, generalized cramping abdominal pains, tenderness, acute distension, and marked prostration. These cases tend to develop gangrene early and run a fulminating course.

(2) *Subacute*: (18 cases) occurring in older age groups, characterized by a more gradual onset of symptoms, history of previous attacks and constipation, and emesis late in the course of the disease. These patients tend to develop gangrene slowly and run a more moderate course.

X-ray is the most helpful aid in diagnosis. Typical findings are: tremendously dilated sigmoid loop situated in the right abdomen, moderate distention of the colon above the volvulus, absence of a collection of fluid within the bowel, "ace of spades" appearance of the barium enema opacity, normal mucosal pattern in the sigmoid and rectum distal to the dilated loop. Volvulus of the sigmoid tends to recur. Exteriorization and second stage resection is the treatment of choice.

FRANCIS D. MURPHY.

SHALLOW, T. A., EGER, S. A. AND CARTY, J. B. Primary malignant disease of the small intestine. *Am. J. Surg.*, 69: 372 (Sept.) 1945.

A study was made of 38 consecutive cases of histologically proven primary malignancy of the small bowel because this problem is rare, difficult for early diagnosis, requires extensive surgical technique, has a high operative mortality and a grave prognosis.

Primary small bowel malignancy occurs in 0.1% of all general autopsies, and it is 36 times more frequent in the colon. Carcinoma in the small bowel is found twice as often as sarcoma, and the ileum ranks lowest for carcinoma and highest for sarcoma. Pathologically, primary carcinomas of the small bowel are divided by their gross morphology into 3 types which in order of frequency are (1) stenosing, (2) infiltrating or ulcerative, and (3) polypoid. Thirty-one of the 38 cases in this series revealed evidence of metastasis to the regional nodes and liver. There were no instances of malignant carcinoids.

The early diagnosis is dependent upon a good history, physical, laboratory and roentgen examination; the latter is the most efficient procedure to date. Lesions of the ampullary portion of the duodenum produced biliary obstruction before intestinal obstruction in all cases.

The type of operation depends upon the condition of the patient, the location and extent of the lesion, and the presence or absence of complications such as jaundice or metastasis. Early and adequate resection, with re-establishment of bowel continuity, is the treatment of choice. Primary malignancy is most favorable in the jejunum and least in the duodenum. The surgical mortality for 27 operated cases was 44%, and the prognosis of sarcoma seemed better than carcinoma. Described in detail is an unusual case of primary adenocarcinoma of the mid-jejunum producing a contact, fistulous communication with the terminal ileum, and requiring extensive surgery which was successfully performed.

MICHAEL W. SHUTKIN.

GILL, A. M. Intestinal mucosa in ulcerative colitis. *Lancet*, 249: 202 (Aug.) 1945.

The author is of the opinion that ulcerative colitis, in some cases, may be due to a deficiency state. Since preliminary investigations suggested that the missing hypothetical factor might be present in or produced by the intestine, the author fed raw pig's small intestine to 5 patients. Three of the five became well and 2 showed no improvement. He then treated 4 additional cases with a simple desiccated defatted pig's small intestinal mucosa (administered by mouth in powder form). Three patients became well and one died after 10 days of treatment. Relapses followed when treatment was discontinued. The extract when given parenterally had no effect.

DAVID J. SANDWEISS.

LIVER AND GALLBLADDER

GILLMAN, J. AND GILLMAN, T. Structure of the liver in pellagra. *Arch. Path.*, 40: 239 (Oct.) 1945.

The authors base their conclusions on the study of some 600 liver biopsies from 120 pellagrins as seen in the hospital of the University of the Witwatersrand Medical School. On the basis of the amount, character, and distribution of fat and pigment, and the presence or absence of cirrhosis, the livers of pellagra patients have been graded into 4 types with certain subtypes. Type I shows the presence of fat deposition only. There are 6 subdivisions depending upon the location and the character of the deposition. Type II contains cystosiderin (hemosiderin) and cytolipochrome (hemofuchsin) in the hepatic and Kupffer cells only. Type III shows deposition of masses of pigment without cirrhosis and Type IV is the same with cirrhosis.

Type I liver tissue changes occur chiefly in acute pellagra of children. According to the authors, they are made worse by treatment with riboflavin, nicotinic acid and thiamine. At times, however, they may be cured clinically and the fat removed from the liver cells by the use of powdered stomach (ventriculin) and a full diet. The various types of tissue changes seen are not clean cut but merge one into another.

Repeated attacks of pellagra show their presence by the remains of former depositions. The authors believe that the pigments are derived from metabolic changes in the mitochondria of the hepatic cell cytoplasm and not from blood elements. They believe that hemochromatosis is the result of such iron pigment changes and deposition, and it is the expression of chronic malnutrition. It is not related to unknown inherited alterations of iron metabolism. They believe, too, that liver cirrhosis, and possibly also the high frequency of primary liver carcinoma in the African natives, is an expression of liver damage due to chronic malnutrition.

N. W. JONES.

BEHRENS M. Congenital atresia of the gallbladder and bile passageways. Report of two cases. *Surg. Clinic N. Am.*, 1242 (Oct.) 1945.

Two cases of jaundice resulting from congenital atresia of the gall bladder and bile passageways are reported. The author makes the general statement that any patient with jaundice lasting more than 4 weeks should have the benefit of an exploration. There are very few exceptions to this rule.

The first case was a 10 month old female infant who was apparently jaundiced at birth. The color deepened steadily. At operation there was absolute obliteration of the hepatic duct. The gallbladder, cystic and common ducts were patent. A drainage tube was placed over the cut into the hepatic duct with the hope that bile would exude following the operation. The baby died following operation, and an autopsy was performed.

The second case was a 5 month old female infant. The baby's skin was noted to be darker than usual at birth. Jaundice was progressive. At operation, the cystic duct, without lumen, was found to be inserted in the liver at its fissure. The hepatic and common ducts were completely closed. A no. 4 ureteral catheter was placed in the bisected gall bladder and the cystic duct. The patient died of biliary cirrhosis 53 days after the operation. Autopsy findings are recorded.

A plea is made for the earlier reference of such cases to the surgeon for operation.

FRANK G. VAL DEZ.

BLUMBERG, N. AND ZISSERMAN, L. Acute suppurative and gangrenous cholecystitis. *Am. J. Surg.*, 69: 38 (Oct.) 1945.

This is a statistical analysis of hospital records collected over a fifteen year period, on cases with a pathologically proven diagnosis of suppurative and gangrenous disease of the gall bladder—with and without perforation. There were 82 cases in the non-perforative and 21 in the perforative group. In about two-thirds, a symptomatic history of biliary tract disease was noted prior to the present attack. The interval between the onset of the present attack of pain and its termination, by either operation or an antecedent demise, averaged 12.75 days in the large group and 9.5 days in the lesser.

The symptomatology, physical signs, and laboratory findings were accentuated in the perforative lesion and generally were in direct proportion to the degree of pathology encountered. The abdominal pain originated either (1) in the right upper quadrant, (2) in the epigastrium, or (3) as a generalized abdominal pain. Radiation of pain occurred in about half the cases and was usually referred to the back, right shoulder, or across the upper abdomen. Marked degrees of tenderness, nausea, and vomiting were common, whereas clinical jaundice was noted in only 10%. Leucocytosis averaged about 15,500 cells; blood chemistry determinations showed few alterations from the normal. Gall stones were found in about 79% of the general group, whereas in the diabetic series of 13 cases the incidence of stone was 77%. The surgical mortality rate was 15.1% but in the diabetics exposed to surgery it averaged 54%, which emphasizes not only the surgical risk for such cases, but that they deserve more prophylactic surgery. The operative technique varied with the need at the moment, but the mortality was greater with cholecystotomy because these patients were the poorer risks.

MICHAEL W. SHUTKIN.

REHFUSS, M. E. AND NELSON, G. M.
Experimental cholecystitis—final results of vaccine and filtrate therapy. *Surg. Gyn. Obs.*, 81: 455 (Oct.) 1945.

A final survey is presented of experimental cholecystitis produced in rabbits by intravenous injection of a viable strain of nonhemolytic streptococcus, originally obtained from a patient suffering from cholecystitis and colitis.

After periods of inoculation and rest, the animals were divided into 3 groups: (1) control, (2) treated with vaccine, (3) treated with a filtrate prepared from the same organism. Any observable difference at necropsy was in favor of the animals who had received vaccine treatment. Of the control group, 64.7% were positive, 4.1% doubtful; of the vaccine group, 44% were positive, 20% doubtful; of the filtrate group, 64% were positive, 8% doubtful. Observation of doubtful lesions may signify a state of involution or the persistence of a low grade infection. In view of the small percentage of doubtful gall-bladder lesions among controls, the evidence favors assumption that the doubtful lesions were undergoing involution. The total positive culture recovery was a somewhat lower number. On the other hand, in a general survey, the evidence of gall-bladder damage was markedly constant in all 3 groups, attesting to the fact that the viable organism was responsible for the changes.

FRANCIS D. MURPHY.

SCOTT, C. C. Observations in total biliary fistula dogs without bile therapy. *Am. J. Physiol.*, 144: 626 (Sept.) 1945.

Four dogs with complete internal biliary fistulae lived for a considerable period of time, apparently in good health, without any bile therapy whatsoever. Diet consisted of dog biscuit and milk. Fat-soluble vitamins were administered parenterally. After developing anemia and losing weight immediately after operation, these animals recovered completely. Studies in some of these dogs showed normal prothrombin time, blood lipids, serum phosphatase, and gastric acidity. No spontaneous hemorrhages, osteoporosis, or peptic ulcers developed. Three dogs have died 16, 25 and 42 months post-

operatively, death resulting from causes other than the bile fistulae. The remaining dog is still alive and appears normal more than 3½ years after operation. The essentiality of bile for the life of the bile fistula animals appears to reside largely in its facilitating the absorption of fat-soluble vitamins.

ARTHUR E. MEYER.

COTTIS, G. W. Treatment of acute cholecystitis. *N. Y. State J. Med.*, 45: 1765 (Aug.) 1945.

The optimum time for operation in acute cholecystitis is highly controversial. The advocates of immediate operation compare acute cholecystitis with acute appendicitis, where delay in operation might result in empyema, gangrene, and perforation. Those who favor delaying the operation feel that the danger of perforation is not nearly as great in acute cholecystitis as in acute appendicitis, and that protective adhesions form quickly which localise the infection in the event of perforation. The author favors an intermediate position, treating each case individually. Acute cholecystitis is nearly always the result of obstruction of the cystic duct by a stone. If the pressure is not great enough to obstruct the circulation, the inflammatory process begins to subside after 3 days. If such does not occur, there is a great danger of gangrene and perforation. If operation is delayed the patient should receive supportive treatment in anticipation of surgery. In simple cholecystostomy, it is essential that the obstruction to the cystic duct be relieved, otherwise there is a danger of mucocele and chronic sinus formation.

PHILIP LEVITSKY.

PANCREAS

ANDERSON, D. H. Celiac syndrome. III.—Dietary therapy for congenital pancreatic deficiency. *Am. J. Dis. Children*, 70: 100 (Aug.) 1945.

For treatment of congenital pancreatic deficiency, the diet should be high in calories, carbohydrate, and protein, but low in fat and starches. Liberal supplements of vitamins A, D, and B-complex must be given. Powdered pancreatin is served in doses of 1 teaspoon (1.5 g.) per meal, mixed with some

convenient solid food. A table of representative diets is presented.

Treatment prolongs survival in cases both of early and of late onset. Prognosis is better for patients with late onset and for those receiving treatment. Seventeen (43.7%) of 38 patients of the treated series are living, and are now aged 1 to 12 years. Dietary therapy should continue through life. In the practical management of these children emotional factors must be considered; over-protection and isolation must be avoided.

IRVING WOLMAN.

ANEMIAS

SCHLEICHER, E. M. Pernicious anemia and miliary tuberculosis of the bone marrow organ. *Am. J. Clin. Path.*, 15: 402 (Sept.) 1945.

The author reports a case of Addisonian pernicious anemia which was complicated by miliary tuberculosis of the bone marrow. The patient was running a low grade fever and did not respond to adequate parenteral liver extract therapy. Roentgen ray examination of the chest did not reveal tuberculosis aside from a Ghon node, and the examination of the sputum was negative for acid fast organisms. However, histologic examination of gross marrow units from the sternum showed several tubercles, in one of which acid fast bacilli were found. Stomach washings also revealed tubercle bacilli in their sediments. The opinion is expressed that possibly the association of tuberculosis and pernicious anemia may be more frequent than has been thought to be the case in the past.

N. W. JONES.

ULCER

INGELFINGER, F. J. AND MOSS, R. E. The therapeutic control of recurrent peptic ulcer. *Med. Clinics N. Am.*, 1162 (Sept.) 1945.

The immediate response of uncomplicated peptic ulcer to medical therapy is excellent. By contrast, the likelihood of a recurrence in 5 years is probably greater than 65%. Emphasis must be placed upon prevention of recurrence of a healed ulcer. No specific means is available for this purpose. How-

ever, the frequency and severity of recurrent peptic ulcer can often be reduced by a practical regimen which opposes some of the factors concerned in the pathogenesis of the disease, but which is not too arduous for the patient to observe. The regimen embodies the following points: (1) education; (2) psychotherapy; (3) dietary management with interval feedings; (4) regulation concerning alcohol, tobacco, and exercise; (5) follow-up observations; and (6) psychological preparedness, so that the patient who is exposed to a circumstance known to aggravate peptic ulcer will adopt an intensified therapeutic regimen before any symptoms develop. The personality of the ulcer patient is discussed.

H. NECHELES.

SANDERS, R. L. A review of 101 subtotal gastrectomies for benign ulcer. *Surgery*, 18: 229 (Aug.) 1945.

In the case of gastric ulcer, the author considers that the indications for resection include chronic perforation, repeated hemorrhage, obstruction and associated extensive gastritis. Resection is also recommended as the treatment of choice in uncomplicated gastric ulcer, since the differentiation between gastric ulcer and cancer cannot always be made. In 22% of the author's cases of gastric cancer, a preoperative diagnosis of ulcer had been made. Resection may also be necessary for uncomplicated gastric ulcer because medical treatment is said to cure no more than 50% of such ulcers.

Resection is recommended as the procedure to be used whenever surgery is indicated for duodenal ulcer, as a result of recurrent hemorrhage, obstruction, intractable pain, and recurrent or reactivated ulcer. For perforation, however, simple closure is advised. The author does not believe in resecting more than one-half of the stomach, unless there is extensive gastritis. He performs a Polya type of antecolic anastomosis and does not do an entero-enterostomy.

This report is a study of 350 operations done on 1,147 patients with duodenal ulcers, 27 operations on 45 patients with gastric ulcer, and 16 operations on 26 patients with gastrojejunal ulcer. One hundred and four of these operations were resections, the use

of resection having increased markedly since 1932. In the last 101 resections the operative mortality was 3% of those patients resected for duodenal ulcer, most satisfactory results were obtained in those with obstruction, next best results were obtained in those who had bled, and the least satisfactory results were noted in those with intractable pain. Of 26 of the last type, complete relief was obtained by only 15.

HENRY TUMEN.

TOSSELAND, N. E. AND McDONALD, J. R.

Ulcerating lesions of the gastroenteric stoma. *Arch. Surg.*, 51: 113 (Sept.) 1945. Following gastroenterostomy for duodenal ulcer, the incidence of ulceration is reported in the literature as varying from about 2 to 4%. In general, the incidence reported for ulceration following gastroenterostomy for gastric ulcer is much less. A detailed clinical and pathologic study is given on cases in which resection of the stomach was carried out for gastro-jejunal ulcer. Parietal cells were seen in the gastric mucosa adjacent to the gastric enteric stoma in the majority of cases. In 81 of the 87 cases in which it was possible to determine the site of ulceration in relation to the anastomotic line, the ulcer occurred on the jejunal side, in 3 on the gastric side, and in 3 on the anastomotic line. Simple epithelial cysts were found at or near the anastomotic line in approximately one-fifth of the cases. Brunner's glands were found occasionally in the jejunal mucosa adjacent to the stoma. The majority of cases showed gastrojejunitis of moderate or severe degree. There was little or no correlation between the degree of severity of the symptoms and the degree of gastrojejunitis. Suture material and magnesium silicate were found in the region of the gastroenteric stoma but appeared to have little direct relationship to the ulcer.

FRANCIS D. MURPHY.

SURGERY

PENICK, R. M., JR. Preoperative and postoperative care of the patient having operations on the gastrointestinal tract. *Surg. Clinics N. Am.*, 1130 (Oct.) 1945.

Laboratory tests to determine accurately the presence of nutritional problems are neces-

sary in diseases of the stomach and intestines. Weight loss, hypoproteinemia, avitaminoses, dehydration, and anemia must all be determined and attempts at their correction accomplished. In preoperative preparation of the stomach and intestines, both small and large, these organs should be relatively empty. Gastric lavage is necessary where any degree of gastric obstruction exists. The use of 0.5% HCl solution in obstructed achlorhydric stomachs is discussed. The rationale of this therapy is to diminish the bacterial flora. In the case of the small intestine, the use of the Miller-Abbott tube is advocated, insertion of the tube being aided by the administration of antispasmodics and water. Preparation of the large bowel with the use of succinyl-sulfathiazole to diminish the coliform bacteria and clostridia is recommended.

In postoperative care, the urinary output remains a reliable guide to adequate hydration. Postoperative ileus is avoided by minimizing trauma to the intestine, and by efforts against bacterial peritonitis. Abstaining from taking anything by mouth, and minimizing swallowing, prevents the ingestion of air and therefore distention. Stimulating drugs such as neostigmine and pitressin, cathartics, and enemas have little value in the treatment of ileus. Diet following operation on the stomach and duodenum should be carefully controlled. Fluids are given in gradually increasing amounts, and suction is indicated if there is any stasis present. Hypoproteinemia must be corrected by plasma and amino acids.

FRANK G. VAL DEZ.

ZINNINGER, M. M. Complications following operations on the gastrointestinal tract. *Surg. Clinics N. Am.*, 1153 (Oct.) 1945.

Infection of the abdominal wound is minimized by covering the skin up to the incision to avoid surface contamination, by irrigation of the wound with saline following peritoneal closure, and by drainage and irrigation of the incision if infection does occur. Where disruption of a wound has occurred, or in potentially infected wounds, through-and-through wire sutures are used, incorporating the entire thickness of the abdominal wall.

Peritonitis is handled by rest to the intestinal tract, reduction of distention by continuous suction drainage, supportive treatment as blood and plasma, maintenance of proper fluid and electrolyte balance, and chemotherapy. If an intra-abdominal abscess develops, drainage is indicated. Ileus in the absence of peritonitis is treated by deflation of the gastro-intestinal tract. Mechanical obstruction is diagnosed by cramp-like pains synchronous with audible peristaltic rushes. Careful reperitonealization of denuded areas at the time of the original operation is emphasized to prevent adhesions of loops of bowel. If obstruction results, re-operation should be performed promptly through the previous incision, provided it be uninfected, and closure with through-and-through suture.

In management of urinary retention, if common conservative measures fail, catheterization every 8 hours with instillation of 0.5% mercurochrome, or use of a retention catheter may be necessary. The value of vitamin K in combatting post-operative hemorrhage in obstructive jaundice is emphasized.

Therapy of fecal, duodenal, pancreatic, and biliary fistulas is discussed. Most post-operative fistulas originate on a mechanical basis, and are more easily cured than spontaneous fistulas which are generally inflammatory. Several cases of fistulas are presented and their management discussed.

FRANK G. VAL DEZ.

SMITHY, H. G., PRATT-THOMAS, H. R. AND MACE, L. M. Reestablishment of pancreatic secretion into the intestine after division of the pancreas: an experimental study. *Arch. Surg.*, 51: 164 (Oct.) 1945.

The authors describe an aseptic technic of implanting the transected uncinat process of the dog's pancreas into the wall of the jejunum. Spontaneous fistula formation developed between the divided pancreatic stump and the jejunum in 71% of the 22 animals, as determined by the appearance of pancreatic juice at the fistula after intravenous injection of secretin.

A low incidence of the usual complications of transection of the pancreas occurred. There was no peritonitis, no external pan-

creatic fistula, 1 retention cyst, and 2 cases of severe acute pancreatitis. All animals survived and remained in good health, whether complicating factors developed or whether pancreaticojejunal fistulas were formed. Fibrous tissue infiltration of the implanted pancreatic stump can occur to a considerable extent without interfering with the secretory function of the gland.

Results suggest application of the method described to patients undergoing radical surgical treatment of carcinoma involving the head of the pancreas and the periaampullary region, for whom preservation of the external secretion of the pancreas is desired.

FRANCIS D. MURPHY.

NEWTON, F. C. AND BLODGETT. Succinyl-sulfathiazole and intestinal suction in surgery of the large bowel. *Surgery*, 18: 200 (Aug.) 1945.

In the preoperative care of patients subjected to colon surgery, the authors use a program which includes saline catharsis, enemas, a low residue, high vitamin intake, and a high caloric diet. Sulfasuxidine is given in a dose of 0.5 g./kg. of body weight the first day, and 0.25 g./kg. daily thereafter, the daily dose being divided into 6 equal parts. The sulfasuxidine is usually given 5 or 6 days preoperatively, but occasionally for as many as 12 days. A Miller-Abbott tube is passed 2 days before operation, and suction is maintained during the passage of the tube. Operation is not performed until the tube end is in the lower ileum. Suction is maintained postoperatively until there is good peristalsis, and the tube is not removed until satisfactory bowel function is established, usually 5 or 6 days after operation.

The author states that after instituting the routine use of the Miller-Abbott tube and of sulfasuxidine, the operative mortality for patients requiring colon surgery was reduced from 19% to 3%, the number of patients with complications was reduced from 58% to 25%, and complications due to local infection was reduced from 43% to 6%.

HENRY TUMEN.

COLE, W. H. AND REYNOLDS, J. T. Resection of the duodenum and head of the

pancreas for primary carcinoma of the head of the pancreas and ampulla of Vater. *Surgery*, 18: 133 (Aug.) 1945.

The authors present a brief review of the various operations which have been advised for resection of the duodenum and head of the pancreas necessitated by carcinoma of the head of the pancreas and ampulla of Vater. They advise a one state resection with transplantation of the common duct into the jejunum, by an end-to-side anastomosis, and performance of an end-to-side gastro-jejunostomy. They note that there is no agreement as to whether or not the stump of the pancreas should be closed tightly or be transplanted into the stomach or jejunum. At present the authors are not transplanting the cut end of the pancreas to the intestines, but in some of their cases pancreatic fistulas have formed. They state that further developments may lead to transplantation of the stump but assert that there is as yet no information indicating that the pancreatic duct will remain open after the stump is transplanted.

The authors present the technique used in five cases. They report one operative death. The other patients are reported to have survived for periods ranging from 6 to 14 months, up to the time of this report.

HENRY TUMEN.

HORGAN, E. The use of a transverse abdominal incision in, and comments on, the surgical treatment of infantile pyloric stenosis. *Surgery*, 18: 339 (Sept.) 1945. The author advocates prompt operative intervention for infantile pyloric stenosis and feels that a large part of the mortality in this condition is the result of delay in operation. Operation should be postponed only long enough to restore fluid and salt balance by the intravenous and subcutaneous administration of fluids and by blood transfusions. Sedatives and gastric lavage or intubation should not be used preoperatively since they increase the incidence of respiratory complications.

The operation recommended is a high transverse incision on the right side between the umbilicus and the ensiform cartilage, with longitudinal incision of the hypertrophied pylorus through the serous and mus-

cular coats. Oral feeding is not resumed until 12 hours after the operation. The first feedings are given at long intervals. Vomiting may occur for a day or two after operation, and the continued use of parenteral solutions may be necessary.

HENRY TUMEN.

PATHOLOGY

MORRIS, H. P. Some nutritional factors influencing the origin and development of cancer. *J. Natl. Cancer Inst.*, 6: 1 (Aug.) 1945.

Of the environmental factors affecting the whole organism and the development of cancer, nutrition is one of the most important. Some of the more specific effects of nutrition on carcinogenesis are as follows. Riboflavin retards the early appearance of hepatic tumors following the feeding of p-dimethylaminoazobenzene, but it appears to increase the number of spontaneous breast tumors in mice. Cystine deficiency delays the appearance of hepatomas induced with p-dimethylaminoazobenzene, but plays only a minor role in spontaneous lung-tumor formation. Dietary fat increases spontaneous breast and epithelial tumors, but inhibits induced sarcomas in mice. Restriction of the diet causes fewer induced sarcomas and epithelial tumors and less spontaneous breast cancer in mice; also if started at an early age, it may completely inhibit mammary carcinogenesis. It also prolongs the life of the experimental animal and modifies the endocrine secretions. A close similarity exists between the neoplastic process and the normal growth processes of the body. Hormonal factors involved in the induction of mammary tumors in mice are also concerned with the normal growth of the mammary glands. When the mammary glands fail to develop, there can be no mammary tumors. Nutrition, therefore, is one important environmental factor. Nutritional factors involved in the origin of experimental cancer are so variable that it seems impossible at the present time to form any general conclusions. Each specific tumor in several species must be studied individually under many different sets of dietary conditions. The effects of poor nutrition on the whole organism are so far-reach-

ing that they may well mean the difference between success and failure in many studies.

H. NECHELES.

PHYSIOLOGY: SECRETION

REHM, W. S. AND ENELOW, A. J. The effect of thiocyanate on gastric potential and secretion. *Am. J. Physiol.*, 144: 701 (Oct.) 1945.

Intravenous administration of sodium thiocyanate in appropriate amounts results in complete inhibition of the secretion of HCl by the stomach, and an increase of the potential difference across the stomach to the resting level. Administration of thiocyanate in smaller amounts results in an inhibition of the secretory rate before the potential increases. Thiocyanate in comparable amounts has no demonstrable effect on the potential of the resting stomach.

ARTHUR E. MEYER.

PHYSIOLOGY: MOTILITY

BOZLER, E. The action potentials of the stomach. *Am. J. Physiol.*, 144: 693 (Oct.) 1945.

The potentials of the dog, cat, and guinea pig stomach were recorded by means of non-polarizable differential electrodes. The approximate shape of the monophasic potential can be derived mathematically from the records obtained. In the dog, the differential potential associated with each peristaltic contraction shows 3 main waves which are designated as R, S, and T waves. The shape of the potential is identical with that of some other visceral muscles and of cardiac muscle, but the complex lasts for 5-8 seconds. During the intervals between each complex there is a period, lasting about 8 seconds, of complete rest. The monophasic potential derived from the differential curves shows a sustained negativity lasting for several seconds. A single shock, applied a few seconds after a T wave, produces a premature peristaltic wave. It is followed by a prolonged pause which is often compensatory. Adrenaline shortens the R-T interval but it stops electric activity only in very high doses. In the cat the same potential as that applied to the dog is obtained as long as the contractions of the stomach are weak. In the guinea pig, a slow potential can be ob-

served only in the region of the pylorus, whereas in the middle portion of the stomach the discharge consists only of brief spikes. It is shown that the potentials observed in visceral smooth muscles cannot be explained on the assumption that the muscle fibers are independent units. The results are in agreement with the conclusion, derived from other observations, that conduction is due to a syncytial arrangement of the muscle fibers.

ARTHUR E. MEYER.

HERRIN, R. C. AND MEEK, W. J. Afferent nerves excited by intestinal distention. *Am. J. Physiol.*, 144: 720 (Oct.) 1945.

Distention of Thiry fistulae in the first portion of the jejunum in otherwise normal, conscious dogs resulted in vomiting and anorexia. Vagotomy did not abolish the vomiting or anorexia during intestinal distention. Bilateral splanchnicotomy and excision of the lumbar chain abolished the vomiting response to distention. Unilateral denervation was not sufficient. The sick impression given by the dog previously was absent following this denervation, but anorexia was present. Splanchnicotomy, vagotomy, and section of the lumbar chains abolished all symptoms due to intestinal distention in 2 dogs, but anorexia remained in 3 dogs. Splanchnicotomy, vagotomy and excision of lumbar chains abolished the anorexia and vomiting when the intestine was distended. It is concluded that the vomiting excited by intestinal distention is entirely of nervous origin and that the nervous impulses are conducted over the sympathetic nerves. The anorexia present with intestinal distention may be due to impulses from the vagi and also from the sympathetic nerves.

ARTHUR E. MEYER.

PHYSIOLOGY: ABSORPTION

FOLLANSBEE, R. The osmotic activity of gastrointestinal fluids after water ingestion in the rat. *Am. J. Physiol.*, 144: 355 (Aug.) 1945.

Adult male white rats were fed 2% of their body weight of water by stomach tube. After a 10-minute period of absorption, samples were withdrawn from the stomach,

duodenum, and jejunum. Two series of animals were employed: one in which the animals were anesthetized after the absorption period was completed, and one in which they were etherized before the water was administered. All of the samples collected from the jejunum were approximately isotonic or slightly hypertonic, while those from the duodenum frequently were hypertonic. The stomach samples averaged 30 m.eq. of sodium chloride per kg. of water. The volumes of fluid recovered agree roughly with those reported in the literature. Less concentrated fluid and larger volumes were recovered from the animals anesthetized before the water was given than from those that were not etherized until later. The water given apparently progressed, in the latter series, farther down the gastrointestinal tract than it did in the former series. Evidence has been presented indicating that the apparent hypertonicity is associated with bacterial activity.

ARTHUR E. MEYER.

VISSCHER, M. B., ROEPKE, R. R. AND LIFSON, N. Osmotic and electrolyte concentration relationships during the absorption of autogenous serum from ileal segments. *Am. J. Physiol.*, 144: 457 (Aug.) 1945.

Measurements have been made of the total osmotic activity, the volume, chloride, acid-labile carbon dioxide, sodium and hydrogen-ion concentration changes in autogenous serum placed in ileal segments of anesthetized dogs. There is rapid absorption of water and chloride from such serum. The sodium concentration falls less while the carbon dioxide content rises. The total osmotic activity falls. The average chloride concentration fall is 36 mM/L in 40 minutes. The average sodium loss is 10 mM/L in the same time. The average total carbon dioxide increase is 20 mM/L. The average net loss of inorganic electrolyte is 13 mM/L, which is identical with the measured decline in total osmotic activity. There is a net absorption of sodium and chloride from autogenous serum in ileal loops, in spite of the fact that initially there are no concentration gradients present, and also in spite of the fact that with time the concentration

in the gut falls much below that in the circulating blood. The developing hypotonicity of originally isotonic solutions in ileal segments was predicted from isotopic tracer studies of absolute rates of movement of water and ions between gut and lumen and blood.

ARTHUR E. MEYER.

VISSCHER, M. B. AND ROEPKE, R. R. Osmotic and electrolyte concentration relationships during absorption of salt solutions from ileal segments. *Am. J. Physiol.*, 144: 468 (Aug.) 1945.

When approximately isotonic solutions of sodium chloride and sodium sulfate in equiosmotic proportions were placed in ileal segments, they invariably became hypotonic to the blood plasma. When 0.001 M mercurous chloride was added to such solutions, the tendency to hypotonicity was virtually abolished. When isotonic sodium sulfate solutions were introduced into ileal segments, such solutions became on the average 2.3 mM/kgm. water hypotonic after 40 minutes, a figure significantly less than that found when sodium chloride was present. The difference is believed to be related to the greater mobility of chloride than sulfate across the ileal epithelium. The net increase in chloride concentration in sodium sulfate solutions was very small, on the average 4 mM/L. in 40 minutes. The addition of 0.001 to 0.002 M calomel or sodium arsenite to isotonic sodium sulfate solutions in ileal segments caused those solutions to become significantly hypertonic, the mean value for osmotic activity being 3.4 mM/kgm. water above the plasma. This was associated with a great influx of chloride. In every case in solutions from which there was a significant water absorption there was definite hypotonicity of the gut solution as compared with the plasma at 40 minutes after introduction of the fluid into the gut segment. It is concluded that when water is absorbed from approximately isotonic solutions of sodium chloride, sodium sulfate, or both, the intestinal mechanism is such that invariably the solutions become hypotonic within a short time.

ARTHUR E. MEYER.

METABOLISM AND NUTRITION

CLARK, D. E., EILERT, M. L. AND DRAGSTEDT, L. R. Lipotropic action of lipocaic. A study of the effects of lipocaic, methionine and cystine on dietary fatty livers in the white rat. *Am. J. Physiol.*, 144: 620 (Sept.) 1945.

Fatty livers were produced in rats by diets rich in fat and low in protein. These fatty livers could be prevented by the addition of 0.5% methionine or of 1.25 to 5.0% pancreas extract (lipocaic). The addition of 0.5% cystine to the diet produced no significant effect on liver fat. Since there was no choline and less than 2% methionine in the pancreas extract, it is concluded that the lipotropic effect of lipocaic on dietary fatty livers in rats must be due to some constituent other than choline, methionine, or the non-specific action of protein.

ARTHUR E. MEYER.

MISCELLANEOUS

BEVANS, M. Changes in the musculature of the gastrointestinal tract and in the myocardium in progressive muscular dystrophy. *Arch. Path.*, 40: 225 (Oct.) 1945.

Four patients with progressive muscular dystrophy came to necropsy and were studied especially from the standpoint of the cause of the so-called cardiointestinal syndrome encountered in some of these patients. Of the 4 patients, 1 died in cardiac failure, 1 from perforation of the stomach and resulting peritonitis, and 2 had marked dilatation of the colon with fecal impaction in one of these. The clinical syndrome consists of vomiting, generalized abdominal tenderness, abdominal pain, diarrhea, tachycardia, and signs of cardiac failure.

Myocardial lesions were present in all 4

cases. They were similar to, but not identical with, those of the skeletal muscles. They consisted of a peculiar distribution of scarring and of areas of muscle degeneration. The more extensive lesions were near the epicardial surface. The amount of fat within the scar tissue was less than that seen in the skeletal muscles. Milder lesions were also seen in the striated muscle of the tongue and upper esophagus. The smooth muscle of the gastrointestinal tract showed edema, atrophy, disappearance of the smooth muscle cells, and occasionally small areas of fibrosis. These changes were not considered specific although they seemed comparable in many ways to those seen in the skeletal muscle. They seemed also to explain some of the clinical symptoms referable to the gastrointestinal tract. The plexuses of Auerbach and Meissner appeared normal, except that they shared in the generalized edema.

N. W. JONES.

FELSENFELD, O. AND YOUNG, V. M. Simultaneous vaccination against bacillary dysentery and cholera with toxoid-vaccine. *Am. J. Trop. Med.*, 25: 421 (Sept.) 1945.

This communication is a preliminary report on experimental studies in the search of a combined vaccine against cholera and dysentery. The vaccine consisted of alcohol treated organisms of *Sh. dysenteriae* and formalized culture filtrate; alcohol killed organisms of *Sh. Paradyenteriae* Y; and phenol killed *V. Inaba*, with formalized filtrates of *Inaba* or *El Tor* strains. Human volunteers were injected and the antibody production was checked by mouse protection tests. The preliminary results warrant further investigation.

PHILIP LEVITSKY.

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VOLUME 6

BALTIMORE, MD.

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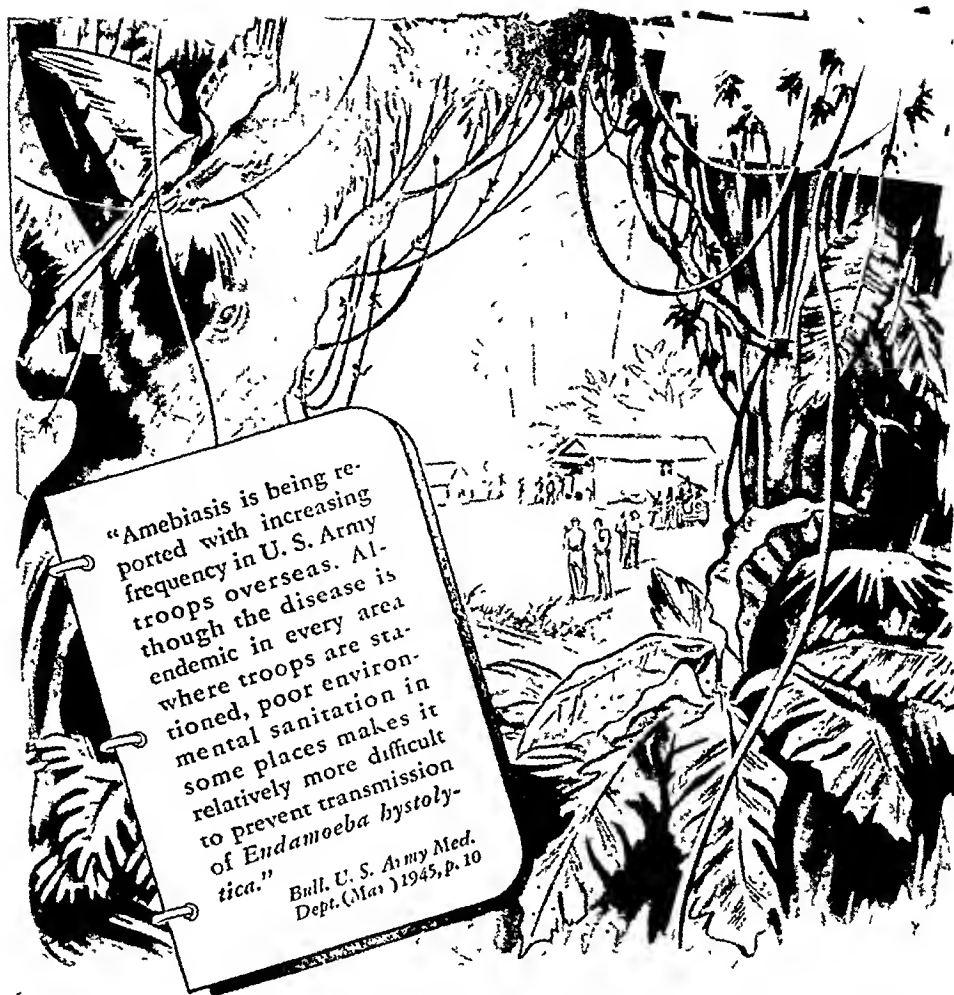
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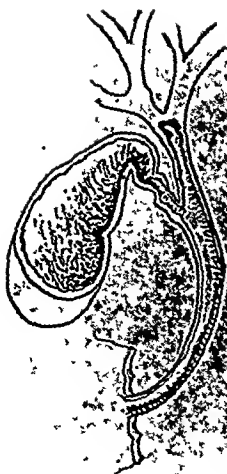
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by Frances Stern

Chief of Frances Stern Food Clinic, The Boston Dispensary, Assistant in Medicine, Tufts College Medical School

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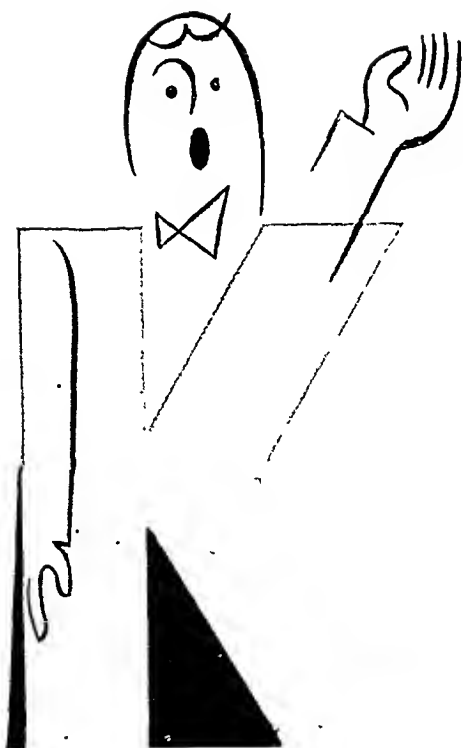
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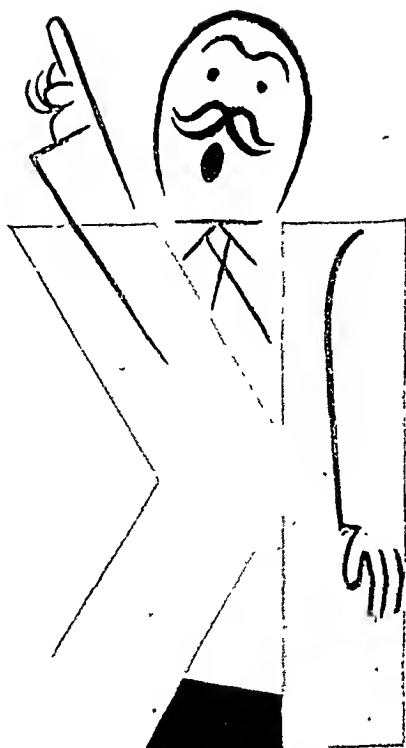


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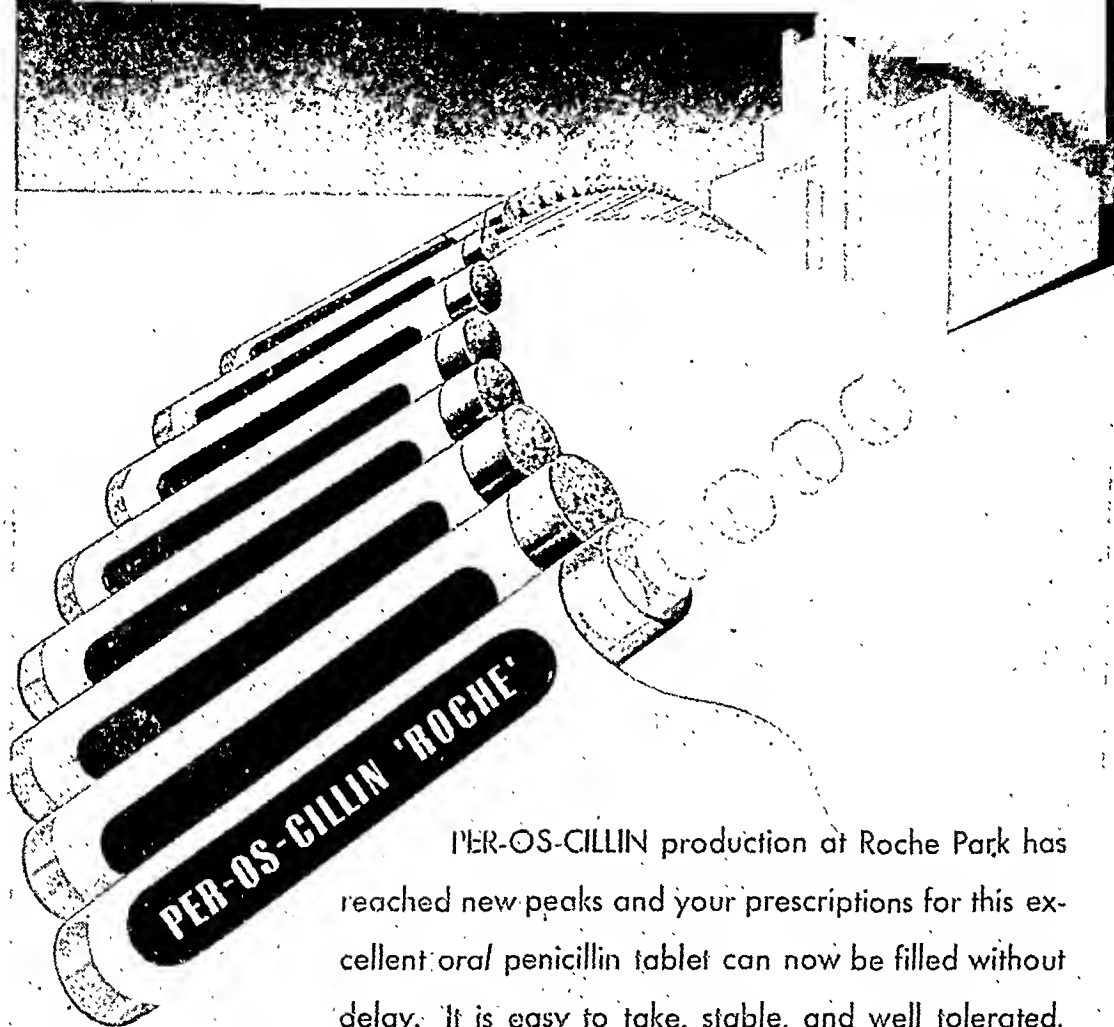


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- (1) Lennox, W. G. (1945), *Petit Mal Epilepsies: Their Treatment With Tridione*, J. Amer. Med. Assn., 129:1069, December 15.
 (2) DeJong, R. N. (1946), *Effect of Tridione in the Control of Psychomotor Attacks*, J. Amer. Med. Assn., 130:565, March 2.